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The Journal of Laboratory and Clinical Medicine

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ORIGINAL ARTICLES

THE BEARING OF ANTITYPHOID VACCINATION ON THE DIAGNOSTIC VALUE OF THE AGGLUTINATION TEST IN TYPHOID AND PARATYPHOID FEVER

BY MAJOR E. RIST, FRENCH ARMY MEDICAL CORPS.

THAT the inoculation of typhoid vaccine causes specific agglutinating properties to appear in the blood of the normal individual is a very well known fact. It is even assumed that the degree and duration of those properties can, to a certain extent, be relied upon to ascertain whether the vaccinated individual is really immune, or, having been immune, continues to be so. To many medical men, however, such an assumption will appear too far reaching. Even in the earlier days of his discovery, Widal had repeatedly shown that agglutinating properties are not immunity reactions and must be carefully distinguished from them. Moreover, the serum of an individual who has previously had genuine typhoid, does not, as a rule, exhibit any agglutinative properties after a year or two have elapsed, unless he happens to remain a permanent carrier; and yet the strongest and most durable power of immunity is the one procured by a previous attack of the disease. Nevertheless, agglutination certainly indicates that inoculation has taken place and has provoked some kind of body reaction; and, as we have no better means of ascertaining it, the complement-fixation test being, as far as this problem is concerned, no more reliable, we have to make use of it, although with due regard to its only relative value.

Now the fact that the serum of a previously vaccinated individual agglutinates B. typhosa must evidently impair the diagnostic significance of the Widal method, and the question arises: if a patient who has been previously vaccinated exhibits clinical symptoms pointing to the possibility of typhoid, are we in a position to make an accurate diagnosis by using the agglutination test?

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If he does not agglutinate, is typhoid to be excluded? If he does, have we any means to prove whether the positive Widal is due to actual infection or to his having been vaccinated? It has been generally assumed that the study of the agglutination titer enables us to do this. In consequence, at least two consecutive quantitative tests should be made at an interval of some days. Many elaborate devices have been proposed in order to facilitate the quantitative estimation of the agglutinative power and to render it more accurate. The Dreyer-Walker method to this effect has even been standardized in the British A. M. C. and has been extensively used in the British Army. Unfortunately when it comes to appreciating the behavior of the agglutination titer and to define the characteristics which belong to the vaccinated-infected type as distinguished from the vaccinated-noninfected, there is no consensus of opinion. Some workers give the foremost importance to chronological considerations, namely to the earlier or later appearance of the agglutinative property or to the rapidity of increase of its titer; others concern themselves with the absolute value of the titer. All, more or less reluctantly, agree to say that there are difficult cases and even cases when the diagnosis based solely upon agglutination is impossible. But they regard those cases as exception, which, on the whole, do not impair the value of the agglutination test.

This is not the only problem raised by antityphoid vaccination. We have to consider also whether previous vaccination against B. typhosus affects, and how it affects, the behavior of agglutination of B. paratyphosus A or B in individuals infected with one of these germs. In other words, does the test enable us to make a correct diagnosis of paratyphoid A or B in a patient who has been previously vaccinated against B. typhosus? This question has also been generally answered in a positive way. One admits that, whether the individual has been previously vaccinated or not, his agglutination titer will be higher with the germ responsible for his actual infection than with B. typhosus. On this matter also, it is generally conceded, however, that there are difficult cases, that sometimes even one may be misled by the agglutination test. Caution is therefore recommended. But on what principles this caution should rest is never clearly stated.

In the rather abundant literature relating to these problems, I have not been able to find out the ground for the assumptions made that (1) there is a specific difference in the behavior of the agglutination titer in vaccinated and nonvaccinated individuals and that (2) the diagnostic value of agglutination of b. paratyphoid A or B remains practically unimpaired by previous antityphoid vaccination. There are, as a matter of fact, *a priori* assumptions, which indeed seem pretty logical and natural at first view, but which nevertheless must be carefully controlled and tested before they can be admitted. The assumption that the difficult and misleading cases are exceptional does not rest on a sounder basis, the only sound basis in the matter being a numerical one.

The percentage of doubtful and mistaken diagnoses—controlled by blood culture—must be ascertained accurately before we can appreciate correctly the practical value of the agglutination test. Only a very low percentage would leave it unimpaired for practical purposes.

I must confess that when I was entrusted, early in 1915, with the typhoid

department of the French military hospital No. 15, in the 6th Army, I myself shared most of the *a priori* assumptions which have just been alluded to. But I determined to control them as extensively as possible, and I propose to give here a short account of my control researches.[1]

During the whole period of my typhoid work (February, 1915-July, 1916) the French Army was being vaccinated against B. typhosus only, the vaccine used being of the Vincent type (culture killed by ether) and four injections at a week's interval being required for a complete vaccination. The inoculations with triple vaccine (B. typhosus and BB. paratyphosus A and B) have been initiated much later.

Blood culture was the routine method of diagnosis in my department, being performed in each separate case, and giving an average of 75 p. 100 positive results. The organisms cultivated from the blood were differentiated on the various sugars and on neutralized, doubtful strains being further tested with high agglutinating specific sera prepared by the Pasteur Institute.

Whether the blood culture was positive or not, the serum of each patient was tested for its agglutinating power with every one of the three germs, B. typhosus, B. paratyphosus A, and B. paratyphosus B. This threefold quantitative test was repeated every second day during the whole course of the disease and, in many cases, during convalescence. The quantitative rates of agglutination were plotted on the temperature chart, enabling us to have a clear view of the behavior of both agglutination and coagglutination in each case.

The method used was the microscopic one, with a twenty-four hour old broth culture of a standard not spontaneously agglutinating germ. The dilution began with 1:50 and went up to 1:100, 1:200, 1:300 and so on until a dilution was found with which no clots of bacilli could be seen. If, for instance, clots were still distinguishable at 1:800 but disappeared at 1:900, the agglutination titer was plotted at 800.

My aim was: (1) to make a careful study of the agglutination curves in all cases where the blood culture was positive, in order to see if a clue could be obtained for interpreting diagnostically the same curves in patients having a repeatedly negative blood culture but exhibiting clinical evidence of typhoid, (2) to study furthermore the behavior of agglutination in a number of evidently nontyphoid patients who had been previously vaccinated against B. typhosus.

The total number of quantitative tests thus performed from February to November, 1915, amounted to 11,648.

I. NONTYPHOID CASES.

Out of 128 positively nontyphoid cases, previously vaccinated, 94 had a positive Widal (76.5 p. 100).

[1]For more detailed statement and tabulation of all the individual cases of my statistics, see: E. Rist, Ftu des sur Fievre Typhoide, I, Annales de Medecine, iii, 54-87, January, 1916.

TABLE I.

	No. of cases	Out of which agglutinated
Angina, acute pharyngitis	8	7
Hypertrophic rhinitis, coryza	15	13
Atrophic rhinitis	1	1
Acute laryngitis	3	2
Maxillary sinusitis	1	1
Pneumonia	13	9
Pulmonary tuberculosis	3	2
Peritoneal tuberculosis	2	1
Meningeal tuberculosis	1	0
Pleural effusion (tuberc.)	4	3
Pleuritis (without effusion)	1	1
Angor pectoris	1	0
Mitral stenosis	1	1
Acute rheumatic fever with valvular involument	4	4
Erythema nodosum	1	1
Lumbago	1	1
Constipation	9	7
Simple diarrhea	12	10
Dysenteric diarrhea	5	4
Amoebic dysentery	2	1
Acute appendicitis	6	6
Duodenal ulcer	1	1
Colitis	1	1
Dyspepsia	1	1
Hernia	1	0
Hemorrhagic jaundice	4	2
Gall stones	1	0
Malaria	11	4
Ephemereal fever of undetermined origin	3	2
Malta fever	2	1
Trigeminal neuralgia	1	0
Shell shock	2	1
Fatigue	6	6

In a majority of cases, B. typhosus alone was agglutinated; but there was also a certain amount of coagglutination; and, in a few instances, one of the paratyphoid germs was agglutinated alone:

TABLE II.

b. typhosus alone	70 cases
b. typh. and para. A plus para. B	2
b. typh. plus para. A	13
b. typh. plus para. B	5
b. para. A alone	2
b. para. B alone	2

The maximum agglutination titer for B. typhosus has varied from 50 to 1500. I have tabulated the percentage of titer in those nontyphoid patients to compare with the same percentage among my nonvaccinated and my vaccinated typhoid patients (See Table III).

The low titers are more frequent in the first group, the high titers in the second and third groups. But the difference is evidently not striking enough to have the slightest diagnostical value. Nor has the titer remained constant

TABLE III.

Agglutination titer	Nontyphoid (90) (vaccinated)	Typhoid (19) nonvaccinated	Typhoid (27) vaccinated
50	18.8%	0	3.7%
100	16.6	10 5	3.7
200	21.1	5.2	11.1
300	13.3	10.5	18.5
400	10	21	0
500	8.8	15.7	3.7
600	3.3	5.2	11.1
700	1.1	0	11.1
800	2.2	5.2	0
900 and over	4.4	26.3	37.7

during the course of observation in every nontyphoid case. One patient, for instance, was admitted with rheumatic fever and valvular endocarditis, temperature 38.8° C. on admission. He was put on sodium salicylate; his temperature went down to 36.6° on the fifth day after admission and continued normal, the pain and swelling of the joints disappearing rapidly. Agglutination titer: first day, 500; third 500; fifth 700; 7th 700; 9th 1,000; 11th 1,000; 13th 1,300; 15th 1,500. In a case of pneumonia the agglutination titer rose from 300 on the day of the critical fall of temperature to 700, 10 days later, when the patient was fully convalescent. In a case of acute rhinitis with laryngitis (temperature normal) the agglutination titer rose within 19 days from 200 to 1,000.

It really seems as if any disease were capable of temporarily increasing the agglutinative power in previously vaccinated people, or of reviving it after it has disappeared. In a case of pneumonia, for instance, the agglutination test proved negative at a 1:50 dilution on the 1st and 3rd days, whereas, on the 5th day a titer of 100 was found, which ultimately rose to 300.

So far we know only of one disease which, instead of increasing or leaving unimpaired the agglutinative properties of individuals vaccinated against typhoid, causes them to disappear temporarily. It is very significant that this singular disease should be measles. This interesting exception, which so curiously confirms the well known anergic influence of measles as regards tuberculous reactions and Jennerian revaccination has been demonstrated for the first time by Leon Bernard and Paraf in 1915.

To return to our subject, I may add it matters little whether the patient has been vaccinated recently or a long time, whether he has received the full dose of vaccine or one injection only. I tabulate here some cases which show this very clearly:

TABLE IV.

Disease	Time elapsed since vaccination	No. of inoculations	Agglutinative titer
Rheumatic fever	5 months	1	600
Malaria	10 months	7	0
Amoebic liver abscess	5 months	1	400
Tonsillitis	7 months	1	300
Laryngitis catarrh	10 days	2	100
Tonsillitis	26 months	5	100
Simple diarrhea	25 months	5	200

I think the facts and figures given in this section justify the conclusion that, in individuals previously vaccinated against B. typhosus, the value of the agglutination test, in order to ascertain whether they are infected with typhoid or not, is absolutely nil. No caution, no niceties of technic, no careful consideration of titer or of the behavior of curves are of any avail whatever.

II. CASES OF TYPHOID AND PARATYPHOID IN PREVIOUSLY VACCINATED INDIVIDUALS.

The cases with positive blood culture which I have studied are:

Typhoid	27
Paratyphoid A	104
Paratyphoid B	35

Typhoid.—All my 27 patients have given a positive Widal with B. typhosus. But in several instances the reaction was found negative during the whole course of actual fever and proved positive only when or after convalescence was reached, namely, for instance, on the 39th, 42d, 44th days. The maximum titers have been moderately high, ranging from 200 to 1800. In one instance the titer never went over 100, and in one other instance over 50.

Coagglutinations were relatively scarce, having been observed in five cases only, which I here tabulate:

TABLE V.

Cases	Maximum agglutination	Maximum coagglutination	
		A	B
1	1200	300	100
2	1400	900	0
3	600	400	0
4	1400	100	0
5	1000	500	500

In case No. 2, the curves of B. typhosus and B. paratyphosus A ran at about the same height during the whole course of the actual disease; it was only during convalescence that B. typhosus predominated distinctly.

In case No. 3 the difference between the level of both curves was very slight and gave no definite impression of a predominance of B. typhosus.

In case No. 5, B. paratyphosus A and, later on, B. paratyphosus B predominated very evidently, until finally the curve of B. typhosus took the lead.

Paratyphoid A.—Out of my 104 patients, 12 (11.5 p. 100) had a constantly negative test for the three germs during the whole course of their disease, none of them having been discharged from my wards before convalescence.

Not more than two patients had a positive test for B. parat. A only, without any coagglutination. The titer in both cases was never over 100.

Contrasting with this, 41 patients (39.5 per 100) had a positive test for B. typh. only, the titer being occasionally quite high (1000, 1700) and the test for parat. A remaining constantly negative.

In one case the test was constantly negative for parat. A and positive for both parat. B and B. typh., the latter predominating. In another case, the test was negative for B. typh. and positive for parat. A and parat. B, the former predominating slightly.

In 24 instances, parat. A and B. typh., and, in 23 instances, parat. A, parat. B and B. typh. were agglutinated. Out of those 47 cases there were only 4 in which the parat. A titer constantly predominated. In 18 cases it ultimately predominated, B. typh. or, to a lesser degree, parat. B having had the lead at the beginning of the disease. In 23 cases B. typh. predominated, namely constantly in 17 and ultimately in 6. In 2 cases, the curves were constantly intertwining and crossing each other at low level, so that no definite predomination could be made out.

It will therefore be seen that out of 104 paratyphoid A infections, with positive blood culture, 6 cases only had agglutinating properties pointing clearly to paratyphoid A (5.7 p. 100). In 18 cases the reaction was misleading during the greater part of the course of the disease, the evidence becoming clearly in favor of paratyphoid A towards convalescence only (17.3 p. 100). In 64 cases the reaction was constantly misleading, the evidence being in favor of B. typh. (61.5 p. 100). In 2 cases the reaction was doubtful all the time, no germ having a decidedly predominating titer.

I give here a tabulated resumé, where A=B or A=T means that the agglutinating titer for parat. A was practically the same as the titer for parat. B, or B. typh., and A>T means that the agglutination titer for parat. A was distinctly higher than for B. typh.

Negative altogether	12	14 = 13.4 p. 100.
A = B or A = T	2	
A positive alone (B and T negat.)	2	6 = 5.7 p. 100.
A>T or A>B (constantly)	4	
A>T (ultimately)	18	19 = 18.2 p. 100.
A>B (ultimately)	1	
T>A (constantly)	23	65 = 62.5 p. 100.
T>B (A negat.)	1	
T positive alone (A and B negat.)	41	

Paratyphoid B.—My 35 cases give the following figures:

Negative altogether	0	5 = 14.2 p. 100.
B = T	5	
B positive alone (T and A. negat.)	0	5 = 14.2 p. 100.
B>T (constantly)	5	
B>T (ultimately)	7	7 = 20 p. 100.
B>A	0	
T B (constantly)	5	18 = 51.4 p. 100.
T B (ultimately)	1	
T and A positive (B negat.)	1	
T positive alone (B and A negat.)	11	

In the paratyphoid B cases, therefore, the agglutination test was unable to give any information whatsoever in 14.2 p. 100 of the cases. It gave early ac-

curate information in 14.2 p. 100, was misleading at the beginning and ultimately correct in 20 p. 100, and altogether misleading in 51.4 p. 100.

If we now sum up all our 166 previously vaccinated typhoid and paratyphoid cases, we get the following figures:

Test negative or uninterpretable	18 (10.8 per 100)
Test altogether misleading	85 (51.2 " 100)
Test first misleading, ultimately correct	25 (15.1 " 100)
Test altogether correct	38 (22.8 " 100)

It is therefore evident that, in vaccinated patients, the chances are for the agglutination test leading to error, however minute the technic, however numerous the tests. It is a remarkable thing—but not unexpected—that the error is always in one direction only: it causes us to mistake paratyphoid for typhoid, but never (as far as my experience goes) typhoid for paratyphoid. We may accordingly pretty confidently assume the diagnosis of paratyphoid A or B to be correct whenever the agglutination titer of one or the other predominates clearly and constantly during the course of the disease. However, we have seen how seldom this occurs (5.7 p. 100 of the parat. A, 14.2 p. 100 of the parat. B cases).

On the other hand, if B. typhosus only is agglutinated or if its agglutination titer predominates—and this is by far the more frequent case—no conclusion whatever can be drawn from the fact. Out of 99 charts where the curve of B. typhosus permanently predominated, 75 belonged to paratyphoid patients. This would put the probability of error to 75.7 p. 100. If we include the cases where the agglutination curve of B. typhosus predominated during the greater part of the actual course of the disease, to be superseded only later on by one of the paratyphoid curves (95 cases) we get 124 charts pointing to typhoid, among which 100 were paratyphoid. This would put the probability of error at the still higher rate of 80.6 p. 100.

III. CASES OF TYPHOID AND PARATYPHOID IN NONVACCINATED INDIVIDUALS.

Although I can deal here only with small numbers, I think it is worth while to compare the figures obtained in the preceding section with those expressing the results of the agglutination test. In nonvaccinated typhoid and paratyphoid patients, treated and observed in the same hospital and during the same period of time.

TYPHOID (22 CASES).

Test negative altogether	3	
T = A or B	0	3 = 13.6 p. 100.
T positive alone (A and B negat.)	17	
T > B (constantly)	1	18 = 81.8 p. 100.
T > A (ultimately)	1	
T > B (ultimately)	0	1 = 4.5 p. 100.
A or B > T (constantly)	0	
A > T (constantly)	0	

PARATYPHOID A (12 CASES)

Negative altogether	4	6 = 50 p. 100.
A = B or T	2	
A positive alone (B and T. negat.)	1	1 = 8.3 p. 100.
A T (constantly)	0	
A > T or B (ultimately)		2 = 16.6 p. 100.
T positive alone (A and B negat.)		3 = 25 p. 100.

PARATYPHOID B (8 CASES)

Negative altogether	2	3 = 37.5 p. 100.
B = A	1	
B positive alone (A and T negat.)	0	3 = 37.5 p. 100.
B > T (constantly)	3	
T B (constantly)	1	2 = 25 p. 100.
T positive alone (B and A negat.)	1	

If we sum up our 42 nonvaccinated cases, including typhoid and paratyphoid, we find:

Test negative or uninterpretable	12 = 28.5 p. 100.
Test altogether misleading	5 = 11.9 p. 100.
Test first misleading, ultimately correct	3 = 7.1 p. 100.
Test altogether correct	22 = 52.3 p. 100.

If we discard the negative or uninterpretable tests, we find:

Test altogether misleading	16.6 p. 100.
Test first misleading, ultimately correct	10 p. 100.
Test altogether correct	73.3 p. 100.

In nonvaccinated patients, therefore, the rate of error is distinctly lower than in vaccinated patients. Here also the error is in one direction only: it leads to mistaking paratyphoid for typhoid, but not to the reverse. Accordingly a constantly positive and predominating parat. A or B test is a reliable argument in favor of paratyphoid, but it is a rare occurrence. On the other hand, a constantly positive T test should be considered with a great deal of caution: out of 23 such curves 5 concerned paratyphoid cases. This puts the probability of error at 21.7 p. 100.

It is interesting to remark that in nonvaccinated cases also, the error is in one direction only. It shows that vaccination against b. typhosus is not the only responsible factor in increasing the agglutinability of B. typhosus in the blood of patients infected with one of the paratyphoid germs. Even in nonvaccinated individuals, an infection with paratyphoid seems to provoke a coagglutinability for B. typhosus which may occasionally be of a higher titer than the specific agglutinability. That this natural tendency is considerably increased by vaccination is obvious.

CONCLUSIONS.

1. In *nonvaccinated* individuals the agglutination test is of the greatest practical value for diagnosing infection caused by the bacilli of the typhoid group.

2. But, when it comes to discriminate between the three subspecies belonging to that group, the information given by the Widal test should be accepted with great caution. A predominance of the agglutination titer of B. parat. A or B speaks almost certainly in favor of paratyphoid A or B. But if the agglutination titer of B. typhosus predominates, the probability of the disease being due to B. typhosus is only 73.3 p. 100.

3. In individuals having been previously *vaccinated* against B. typhosus, the agglutination test is absolutely unable to confirm a clinical diagnosis of typhoid. The behavior of the agglutination titer in vaccinated typhoid or paratyphoid patients is not distinguishable from the behavior of the same titer in vaccinated individuals suffering from any other disease.

4. In a case of clinically confirmed typhoid occurring in a previously *vaccinated* individual, the agglutination test has a practical diagnostic value whenever it shows a constant predominance of the agglutination titer for one of the paratyphoid germs. But this is a very rare finding. In the greater majority of cases the agglutinating titer for B. typhosus predominates. It has no diagnostic value whatever, the probability of mistaking paratyphoid for typhoid being 75.7 p. 10.

5. Blood-culture is therefore the only reliable method to ascertain whether a typhoid infection occurring in a vaccinated individual is due to B. typhosus or to one of the paratyphoid germs.

ANTIBODIES IN GONOCOCCAL ARTHRITIS AFTER THE INTRAVENOUS INJECTION OF SPECIFIC AND NONSPECIFIC PROTEIN*

By Harry Culver, M.D., Chicago, Ill.

WHEN a suspension of bacteria or a pure protein solution, such as primary or secondary proteose, is injected intravenously into an individual, there occurs a clinical reaction quite similar in every instance regardless of the bacteria or protein solution used, once the proper dosage is established. This reaction takes place in a normal individual as well as in one suffering from infection.

The reaction is characterized by a chill of variable severity, coming on usually within one hour following the injection, coincident with which there is, as a rule, a marked decrease in leucocytes in the peripheral circulation, as well as a drop in temperature. This condition lasts for twenty to thirty minutes, when the chill abates and the temperature of the individual gradually rises, reaching its climax in four to six hours. At this time there is usually profuse perspiration and a considerable increase of leucocytes in the peripheral circulation. The temperature and number of leucocytes in the peripheral circulation return to normal in twenty-four to forty-eight hours.

These reactions have been used, with success, in the treatment of gonococcal arthritis, epididymitis, and acute prostatitis.[1] In some instances of typhoid fever a critical fall of temperature, with rapid recovery of the patient, has been observed immediately following a similar reaction. This has taken place both with specific typhoid organisms and with nonspecific substances like colon bacilli and proteose solutions. Equally striking results have been seen in obscure respiratory infections associated with remittent fever.[2]

A pronounced feature of the action in gonococcal infections is that the most marked benefit, both subjectively and objectively, occurs within twenty-four hours following the first injection. Subsequent injections may cause some therapeutic response, which is usually not to be compared with that following the first injection.

That marked beneficial therapeutic results follow the injections in many instances of gonococcal infection there seems to be no question. The factors that should be considered in the mechanism of the improvement or recovery and which have been discussed by various investigators, are the production of fever, peripheral leucocytosis, profuse perspiration, disturbance of the ferment antiferment balance, and the mobilization of fixed antibodies.

This work was undertaken to determine if there is a specific antibody response for gonococci after the injection of nonspecific proteose solutions comparable to that which is produced by the injection of killed gonococci in gonococcal arthritis; also to determine what place, if any, antibody production or mobilization, has in the marked objective and subjective improvement seen in cases of gonococcal arthritis within 24 hours after a protein reaction.

Dreyer, Gibson and Walker[3] have found that paratyphoid fever B commonly

*From the Department of Experimental Medicine University of Illinois, Chicago, Ill.

causes a rise in the typhoid agglutinin titer, frequently considerable, while paratyphoid fever A causes a less pronounced increase. Meyer and Christiansen,[4] by infecting a rabbit with tuberculosis noted that its serum possessed agglutinin for typhoid and the animal also gave a good typhoid intracutaneous reaction; while Conradi and Bieling[5] have observed that any intercurrent infection is liable to increase the typhoid agglutinin of the serum of any individual who has ever had typhoid or been vaccinated against it. Dunklin,[6] working with typhoid immune rabbits, noted an increase in the agglutinin for typhoid bacilli in the serum of these animals after an intravenous injection of proteose solution. Ludke[7] on the other hand, states that there is no change in the agglutinin content of serum of typhoid patients, for typhoid bacilli, after the intravenous injection of secondary proteose.

Bull[8] found that within twenty-four hours after an intravenous injection of killed typhoid bacilli in normal and typhoid immune rabbits, there is an increase in lytic substances for typhoid bacilli in the serum. Teague and McWilliams[9] repeated and extended Bull's work and conclude that the bacteriolytic power of the serum of normal and immune rabbits for typhoid bacilli is neither increased nor decreased by a large intravenous injection of killed typhoid bacilli, while the serum of a rabbit that has received only one or two immunizing injections shows a distinct but not a great increase in its bactericidal power within twenty-four hours after such an injection.

The opsonins and bactericidal substances were studied in the serum of sixteen patients suffering from gonococcal arthritis. An injection of killed gonococci or proteose solution was given intravenously every seventy-two to ninety-six hours until three to five injections had been given. The serum was taken for study just before each injection. Ten of these patients received successive injections of proteose and six received killed gonococci. No marked difference was seen in the results of the two groups.

The opsonin content was determined by the extinction method as described by Klein.[10] The bactericidal substance in the serum was determined by the dilution method; i.e., the bactericidal titer of the serum is represented by that dilution of the serum which causes an appreciable decrease in the number of colonies upon plating, from the different dilutions, at successive intervals, a normal control serum being always used at the same time. Teague and McWilliams[9] and before them Buxton[11] concluded that the bactericidal titer of an immune serum for typhoid bacilli as determined by the usual dilution method, with or without the addition of complement, is not an indication of the bactericidal power of the blood plasma *in vivo*. However, with so delicate an organism as the gonococcus, this method gives more regular and more readily comparable results than by the use of a method in which a standard amount of serum is used for a standard time in contact with a known constant number of gonococci and the action of the serum determined by plating at regular intervals. Since only three to five successive injections were given each patient, the factor of a too highly immune serum being developed, seldom interfered. If, however, after several successive injections it was found that the patient's serum would fail to kill in concentrated serum solution, but would kill in less concentrated solutions, it was invariably found that the killing zone had moved

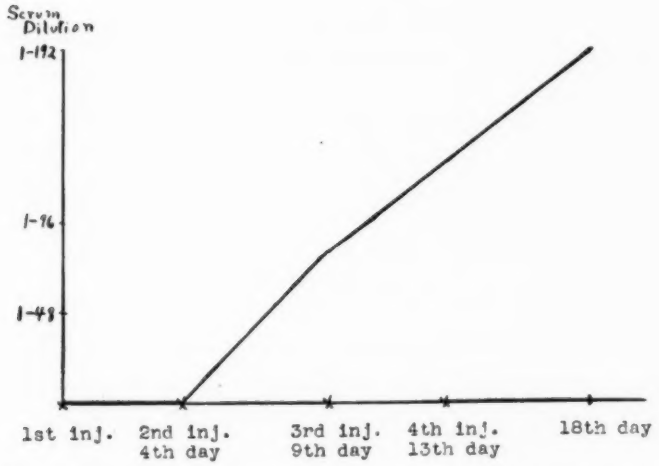

Chart 1.—Opsonin curve after the intravenous injection of killed gonococci.

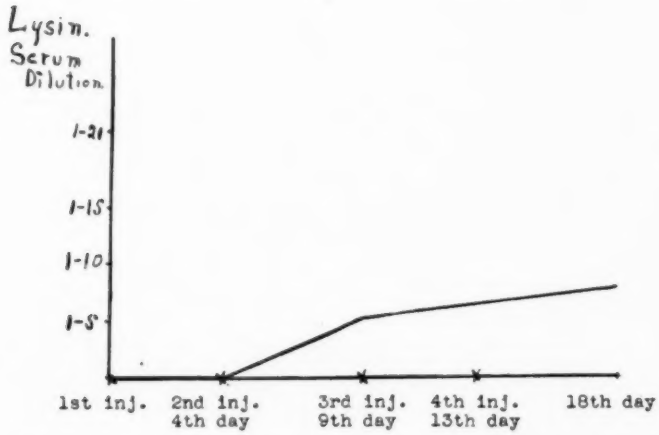

Chart 2.—Lysin curve of same serum as represented in Chart 1.

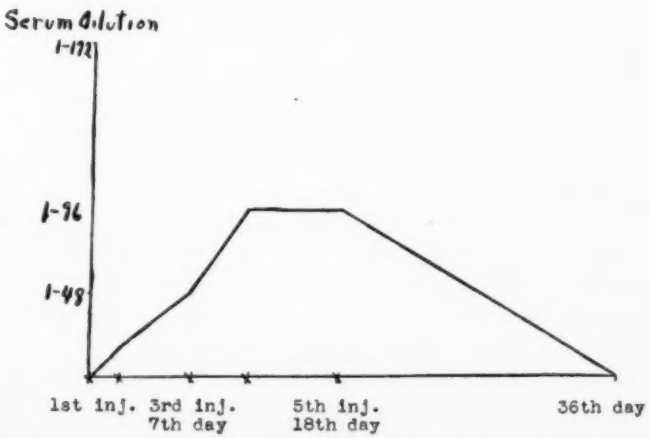

Chart 3.—Opsonin curve after the intravenous injection of secondary proteose.

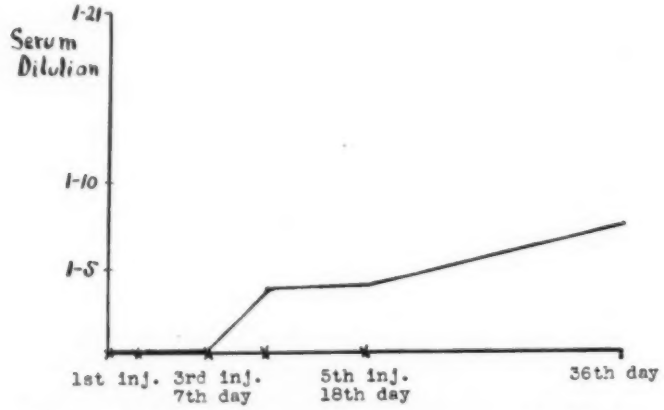

Chart 4.—Lysin curve of the same serum as represented in Chart 3.

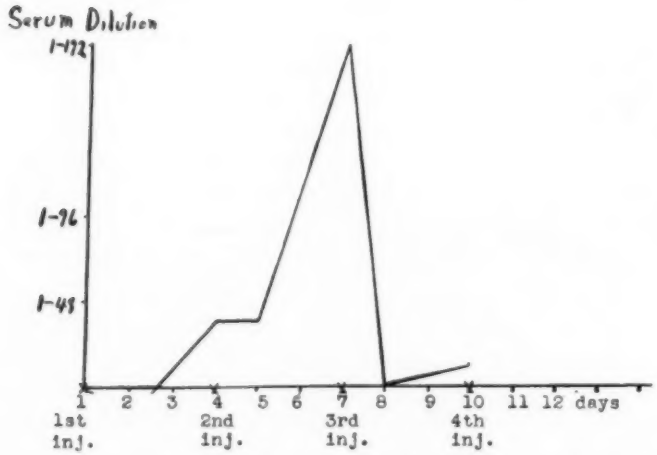

Chart 5.—Opsonin curve of serum taken just before, and 24 hours after, successive intravenous injections of killed gonococci.

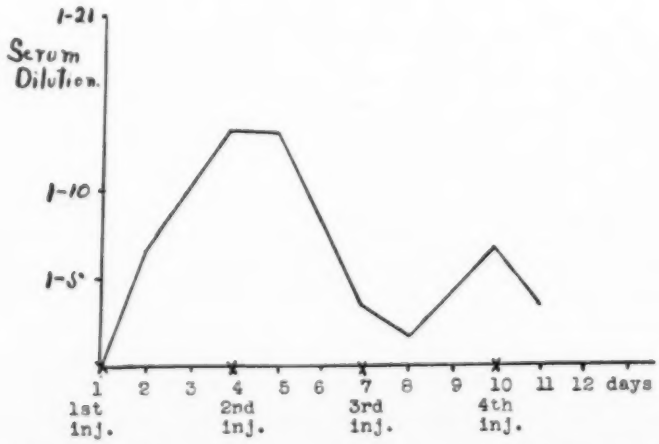

Chart 6.—Lysin curve of the same sera as represented in Chart 5.

to a serum with a greater dilution than before the pro-killing zone developed. In these instances the bactericidal titer is considered the highest dilution of the killing zone.

The serum to be tested was successively diluted with nutrient broth. To a standard amount of each serum dilution was added a drop of a standard suspension of gonococci twenty-four hours old. A loop of material from each tube was plated at once and serum mixtures incubated at 37° C. for four hours when a second loop of material was plated from each dilution. The plates were

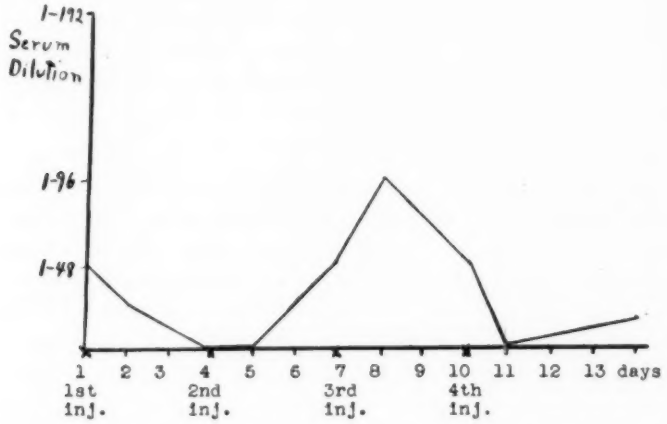

Chart 7.—Opsonin curve of serum taken just before, and 24 hours after, successive intravenous injections of primary proteose.

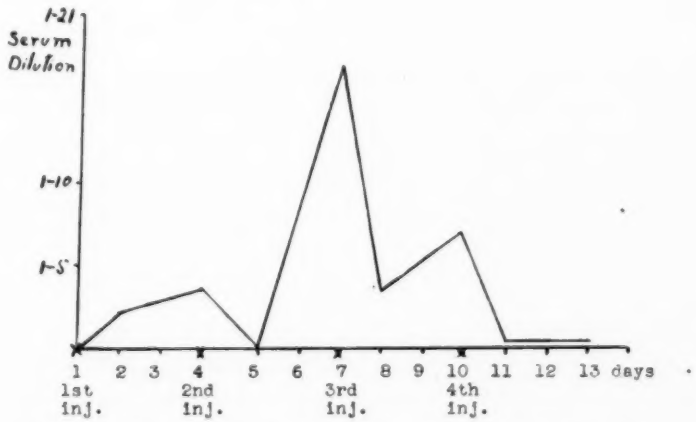

Chart 8.—Lysin curve of the same sera as represented in Chart 7.

incubated for forty-eight hours and then all colonies were counted on each plate. A comparison of these results was then made to determine the highest dilution in the killing zone. It was found at the beginning of this work that the fresh serum to be tested was sufficiently complemented to cause bacteriolysis even in the highest dilution 1:64. Hence it was not necessary to inactivate and reactivate each dilution with a known amount of complement.

Antibody response after injections of specific substances is known to be very variable in different individuals and in the same individual at different times.

After a careful study of sixteen patients, however, there was noted no appreciable difference between the antibody production following killed gonococci injections and proteose solution injections. This fact can best be shown graphically in any two cases as in Charts 1, 2, 3, and 4. These charts clearly show the increase in opsonin and lysin of the patient's serum for gonococci after the injection of dead gonococci and proteose solutions. There is no distinguishing feature in these curves by which the injected material could be recognized. The opsonin reached the highest point after the injection of gonococci, while the lysin curve rises after the injection of proteose. However, these conditions may be reversed with any other two cases similarly traced. This antibody response is variable but present to some degree in every patient of the sixteen injected, whether the material injected was specific gonococci or nonspecific proteose and also regardless of the therapeutic response obtained.

In a second series of six patients, three were treated with injections of killed gonococci and three with primary and secondary proteose solutions, the serum of each being tested just before and twenty-four hours after each injection, at which time the most pronounced therapeutic effect is present. Charts 5, 6, 7 and 8 show the antibody curves for two typical cases and represent the usual findings of a slight increase in lytic substance following the first injection, whether gonococci or proteose and a corresponding decrease in opsonin. All succeeding injections cause either a decrease or no change at all in both lysin and opsonin during the first twenty-four hours following the injections. An unusual condition occurred in Chart 8 where there is seen a moderate rise in opsonin within twenty-four hours following the third injection of proteose.

COMMENT.

By the methods above outlined it was found that both the opsonic and bacteriolytic titer of the serum of patients suffering from gonococcal arthritis were approximately normal or below before any injections were made. This has been previously observed by Irons[12] and others for the opsonin content of serum from these patients. He also demonstrated that spontaneous fluctuations in antibody content occur in gonococcal arthritis and that by massage of the affected joints or the infected prostate there resulted an opsonin increase not altogether unlike that produced by an injection of killed gonococci. Therefore any antibody change which results from an injection of a substance which produces a chill might well be explained by the motion of the affected parts during the chill. Since the curves regularly show an increase in lysin and a decrease in opsonin after the first injection and reaction, while each succeeding injection is usually followed directly by an antibody decrease regardless of the intensity of the reaction, it does not seem that the joint motion has much to do with it here. The above antibody changes occur in serum of patients with acute, subacute, or chronic joints with no appreciable difference between these classifications; which might be expected were the antibody changes due entirely to motion of the affected parts. Some sera have been studied after a small amount of protein was injected, a large enough amount to increase the leucocytes and temperature but not sufficient to produce rigor. These injections were followed by antibody changes not unlike those produced by the more severe reactions.

SUMMARY.

Primary and secondary proteose preparations stimulate antibody production or mobilization for specific organisms in gonococcal arthritis, in a manner not to be distinguished from that produced by the injection of the specific organisms themselves.

In gonococcal arthritis, there is either no change or a decrease in the antibody content of serum within the first twenty-four hours following an intravenous injection, in all excepting the first injection when the lytic substances seem to be slightly increased during this time.

In favorable patients the first injection usually causes the greatest clinical benefit. However, refractory patients may give a similar lysin increase during the first twenty-four hours following an injection; hence the subjective and objective improvement in favorable cases can not unquestionably be attributed to an increase in antibodies alone. However, little as these substances may have to do with the early relief of symptoms in gonococcal arthritis, it may be that they have considerable to do with the final recovery from the infection by their influence upon the primary focus.

It would seem that there is no one particular factor which is responsible for the benefit derived in favorable patients, but a series of events occur, which, when acting together or in succession, tend toward the relief and ultimate recovery of the individual from the infection.

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OBSERVATIONS ON THE BLOOD AND URINE AMMONIA IN ACIDOSIS*

By H. L. McNeil, M.D., and M. D. Levy, M.D., Galveston, Texas.

THE following investigation was undertaken as a result of the accidental discovery of an unusually high ammonia content of the blood in a male patient, a chronic alcoholic, who was suffering from repeated periodic attacks of nausea and vomiting of unknown etiology, the attacks having commenced without any apparent cause. Although the etiology of the vomiting in this case was unknown, the fact that the patient, a man fifty years of age, was a chronic user of whiskey in rather large amounts suggested some connection between this fact and his symptoms. There was no evidence of nephritis or of any other pathologic lesions to explain his symptoms. (This case has elsewhere been reported in detail.[1])

During the course of routine analyses of the blood of this patient for urea, an estimation of his blood ammonia was made, which showed an ammonia content of 23 mg. of ammonia per 100 c.c. of blood. Suspecting an error in technic as the explanation of this high ammonia content, numerous subsequent estimations of blood ammonia were made on different days, all of which showed a marked increase. These ammonia estimations were made after the aeration method of Folin, using 1/50 N. sulphuric acid to absorb the ammonia and titrating this against 1/50 N. sodium hydroxide with alizarin as an indicator. As a further control on these estimations numerous similar estimations were carried out on other patients at the same time, as well as on seven normal individuals, and in none of them was any abnormal amount of blood ammonia demonstrated. A reference to the protocol will show that on four subsequent occasions 16, 12, 8, and 3 mg. of blood ammonia were found, while as the condition of the patient gradually improved other estimations showed that the excess of blood ammonia had disappeared.

A search of the literature upon the subject of blood ammonia in normal and diseased conditions reveals comparatively few satisfactory studies. Since the more accurate methods of estimating ammonia in the blood are comparatively recent, one can accept only with great reservation the observations made before the methods of Folin were introduced. A few apparently authentic, isolated instances of increased blood ammonia in human beings have, however, been reported in cases of acidosis. In these cases, practically none of which are given in sufficient detail to be of much real value, it was believed that the blood ammonia increase was a compensatory phenomenon resulting from the increase in the acid radicals of the blood during acidosis. A number of isolated cases are also mentioned in the literature in which an increase of blood ammonia was found in association with eclampsia, uremia, acute yellow atrophy of the liver, phosphorus poisoning, and in the terminal stages of cirrhosis of the liver. In practically all of these instances, however, the ammonia increase was ascribed to acidosis. On the other hand, numerous careful studies upon the chemistry

*From the Department of Internal Medicine, University of Texas Medical School, Galveston, Texas.

of the blood in such conditions have failed to show any constant increase in blood ammonia although an increased ammonia coefficient of the urine is known to be commonly present in certain diseases of the liver, as in some cases of eclampsia, in acute yellow atrophy of the liver, and the pernicious vomiting of pregnancy.

In this connection the well-known work of Pawlow and his associates[2] done many years ago upon Eck fistula dogs, which showed symptoms of toxemia upon high protein diets, is of interest. While the observations of these observers is now somewhat discredited so far as their studies of the blood ammonia in these toxic animals is concerned, the methods which they used for estimating ammonia having been open to question, nevertheless, their claims as to increased ammonia percentages in blood and urine of these intoxicated animals is of interest. Fischler[3] has also, more recently, put forward similar claims in accounting for protein intoxications in Eck fistula dogs whose livers have been thrown out of the portal circulation, basing his claims, however, upon an excess of ammonia in the urine rather than the blood.

In the present state of our knowledge regarding the relation of increased blood ammonia to disease, a study of the literature would, in short, suggest that a condition of acidosis is usually present when such increases are noted. The same explanation would be the apparent explanation also, for increases of ammonia excretion in the urine in most cases, although the work of Williams,[4] Losee and Van Slyke,[5] and others would seem to indicate that an *increased ammonia coefficient in the urine* may occur in the pernicious vomiting of pregnancy without the accompanying acidosis.

BLOOD AMMONIA CONTENT IN NORMAL INDIVIDUALS.

As has been stated, the observations upon the blood ammonia of both human beings and animals, carried out by the older observers, are open to question due to the more or less inaccurate technic. The development of the methods suggested by Folin[6] have, however, enabled the observer to carry out blood ammonia estimations in a comparatively accurate manner. All recent observers, using Folin's methods or a modification of the same, are now apparently agreed that the blood ammonia in normal men and animals never exceeds 1 mg. per 100 c.c. of blood. In fact 1 mg. per 100 c.c. may be considered as the extreme upper limit for blood ammonia. Medwedew[7] has, for example, found an average content of 0.56 mg. per 100 c.c. in normal dogs. Rhode[8] found the ammonia content of dogs to vary between 0.17 and 0.72 mg. per 100 c.c. Gettler and Baker[9] found an average of between 0.4 and 0.75 mg. per 100 c.c. of blood in 30 normal human beings. Bennett,[10] using a different technic, found an average blood ammonia content in five normal men of only between 0.07 and 0.1 mg. per 100 c.c. Finally Folin and Denis[11] have always found less than 1 mg. per 100 c.c. in both men and animals as the ammonia content of the systemic blood.

In carrying out routine examinations upon the blood for its ammonia content, however, it is necessary to bear in mind the very important fact that blood after its withdrawal quickly shows an increase in its content of ammonia, apparently due to the decomposition of certain nitrogenous bodies which are normally present in it. Accordingly, unless estimations for ammonia are made promptly after the withdrawal of blood, the real values of ammonia can not be

obtained. That the production of ammonia in blood which is allowed to stand after being withdrawn must be considered as an important factor in such estimations is shown by the work of Medwedew,[7] who found that after standing for 24 hours, the ammonia content of the blood of dogs would rise from normal to as high as 2.93 mg. per 100 c.c. It was shown, moreover, that the ammonia formation began within a few minutes after the withdrawal of the blood. This observation has since been confirmed by Folin and Denis, Rhode,[8] and others. During the course of our own investigations, we also have found the same to hold true of human blood. In no instances, however, have we found the ammonia content of sterile normal blood to rise above 3 mg. per 100 c.c., even after prolonged standing, nor have any of the observers mentioned above found the rise in ammonia to exceed this limit after standing. Apparently, therefore, the normal upper limit for ammonia in perfectly fresh blood may be taken as 1 mg. per 100 c.c., and under any circumstances, with a proper technic, a finding of over 3 mg. per 100 c.c. may be safely taken as abnormal.

TECHNIC OF ESTIMATIONS.

In the following studies an effort has been made to make the technic as uniform as possible. The blood has been examined immediately after its withdrawal into thoroughly cleansed tubes, to which was added 1 c.c. of a 2 per cent citrate solution to prevent clotting. The aeration method of Folin was used, brisk aeration for one-half an hour being applied, and the ammonia which was blown over being collected in a 1/50 N. solution of sulphuric acid. This was then titrated from a microburette with 1/50 N. sodium hydroxide, using an aqueous solution of alizarin as an indicator. Since, from a clinical standpoint, only comparatively marked variations in any chemical element of the blood can be considered of any practical diagnostic significance, an attempt was made in these observations to detect only those increases of ammonia which exceeded 1 mg. per 100 c.c. of blood, and in the following tables all amounts of 1 mg. and under are expressed as a "trace." Also, all amounts up to 3 mg. per 100 c.c. have been considered as possibly due to changes attributable to variations in technic, although it is our belief that the technic was not responsible for such increases.

In order to remove, as far as possible, the factor of diet from the results of these examinations, an effort was made to place all patients, whenever possible, upon a diet consisting of 32 ounces each of milk and albumin water per 24 hours for at least 24 hours preceding the examination, the above diet constituting the ordinary hospital liquid diet. Our experiments upon normal individuals would seem to show, however, that at least in normals, diet has no influence upon ammonia increases since, of our seven normal individuals, all of whom showed less than 1 mg. per 100 c.c., all were purposely placed upon high protein diets preceding the tests.

The alveolar air estimations for CO_2 tension were carried out after the method of Fridericia.[12] Acetone and diacetic acids were estimated by the sodium nitroprusside and the ferric chloride tests, respectively. The bicarbonate test of Sellards[13] for acidosis was considered positive when it required more than 15 gm. of bicarbonate taken by mouth to alkalinize the urine. The blood urea

estimations were carried out after the method of Van Slyke and Cullen, using Marshall's urease method to decompose the urea. Five cubic centimeters of blood each were used in the estimations of both urea and ammonia.

DISEASES STUDIED.

Our findings as to the blood ammonia content in various pathologic conditions may best be considered, perhaps, by a consideration of the diseases in separate groups. The clinical diagnoses in the following cases have been made as carefully as possible by modern clinical methods and in a considerable percentage of cases the diagnoses have been confirmed by autopsy.

NEPHRITIS.

As will be seen from the protocol, 19 cases of nephritis have been studied. Among these cases are included the various types of nephritis which are met with clinically, both the high tension cases with moderate edema and those types characterized by general anasarca with only slight urea retention being represented. In this series are included also, four cases dying, of uremia, as well as several mild cases. As will be seen from the protocol, three cases in this series showed increases in blood ammonia which might be considered marked (over 3 mg. per 100 c.c.). It is interesting to note that none of the four uremics showed such blood ammonia increases. It is also of note that all three of the cases showing an excess of blood ammonia were also complicated by myocarditis with definite evidence of cardiac failure and with chronic passive congestion of the visceral organs. All three of these cases showed definite evidence of acidosis.

CARDIAC FAILURE.

In addition to the cases of cardiac disease included in the nephritic series, fourteen other cardiac cases were studied, not complicated by nephritis. Four of these showed blood ammonia in quantities of over 3 mg. per 100 c.c. It is of interest to note that all of these cases also showed evidence of acidosis, and that all were suffering from chronic passive congestion of rather marked degree, several having pulsating livers. It should be mentioned that while all of the four cases showing blood ammonia increases in this series, also gave evidence of acidosis, nevertheless, several other cases in which the acidosis was just as severe failed to show blood ammonia increases.

CHRONIC DISEASES OF THE LIVER.

In view of the close relation supposed to exist between the liver and the normal metabolism of the proteins, and in view of the apparently close connection between the liver and the conversion of the ammonia formed by protein metabolism into urea, one would expect theoretically to find evidence of accumulation of ammonia in the blood in serious diseases of that organ. As a matter of fact, however, reference to the protocols will show that such is apparently not the case, at least in chronic diseases of the liver. In only one of such cases studied in this series has any definite increase of blood ammonia been found, this being a case of syphilis of the liver, with severe toxemia, whose blood was

examined just before death. In this series, as will be noted, were included four cases of Laennec's cirrhosis of the liver, three cases of syphilitic cirrhosis, one case of amebic abscess of the liver, and two cases of rather marked jaundice. Chronic diseases of the liver may be said, therefore, to have no definite and constant connection with increase in blood ammonia.

TOXEMIAS OF PREGNANCY.

In connection with disease of the liver the few observations which we have been enabled to carry out upon several forms of toxemias occurring during pregnancy may be of interest, since at least certain forms of such toxemias, such as the pernicious vomiting of pregnancy and eclampsia are well known to be associated with acute hepatic lesions, and with increased ammonia coefficients in the urine, as was first emphasized by Williams.[4] In this series three cases diagnosed clinically as probable cases of eclampsia, and one case suspected of being the pernicious vomiting of pregnancy, were studied. It is interesting to note that two out of three of the cases diagnosed as eclampsia showed definite blood ammonia increases, while one case of persistent vomiting complicating pregnancy showed a somewhat less marked increase. It is also of interest that one of these cases, showing an increase in blood ammonia, failed to show any evidence of acidosis. Also, one case of this series, which had shown a marked increase in blood ammonia, coming to autopsy, showed the typical hepatic lesions of eclampsia.

ACIDOSIS.

Thirteen cases of acidosis from various causes other than cardiorenal disease have been studied in this series. The majority of these cases were characterized by the severity of the acidosis. Six of them were diabetics. One was a case of diabetic coma. In spite of the fact that most of these cases of acidosis were characterized by their severity as determined by their symptoms and by the usual tests for acidosis, one is surprised to note the small percentage of cases showing marked increases in their blood ammonia. Only two out of thirteen cases showed marked blood ammonia increases. Both were postoperative cases, one being a case of general peritonitis, which at autopsy showed a rather marked cloudy swelling of all organs, and in addition, showed marked fatty degeneration of the liver. The other case was one of persistent nausea and vomiting following a laparotomy. The nausea and vomiting at the time of the blood examination had persisted for three weeks, and was evidently not the ordinary type of postoperative vomiting. The vomiting in this case was suspected of being of nervous origin, although it was severe enough to cause a rather serious condition clinically. The patient recovered, however. It is of interest in connection with these cases of acidosis, to note that blood ammonia is apparently by no means proportional quantitatively to the severity of the acidosis, since the severest cases of acidosis noted both in the cases included under acidosis, as well as in the cases of acidosis complicating heart and kidney diseases, were not as a rule the ones showing the highest blood ammonia content. Moreover, it is of interest that the single case of diabetic coma with unusually severe acidosis, studied in this series, failed to show any marked increase in blood ammonia, although the *urine*

did contain a marked excess of ammonia. The well-known fact regarding the relation of acidosis to an increased content of ammonia in the urine was also confirmed in those cases of acidosis in our series, in which 24-hour urine specimens could be obtained.

DISCUSSION.

As stated above, from our observations, there would seem to be no definite connection between the severity of the acidosis and the high ammonia content of the blood, although the connection between acidosis and the high content of the urine ammonia is evident. Moreover, at least two cases observed by us, whose blood contained an excess of ammonia, failed to show any definite evidence of acidosis as determined by the usual tests, as well as by clinical signs.

In Case No. 69, which showed a rather large percentage of urine ammonia without a corresponding increase of blood ammonia, we have made an effort to determine, if possible, the reason for this discrepancy. In this case the ureters of each kidney were catheterized, and the fresh urine, immediately after its excretion from the kidney, was analyzed for ammonia. In this case, a case of severe diabetic acidosis, to our surprise, the smallest amount of ammonia was found in the absolutely fresh urine, only 5 mg. per 100 c.c. being noted, whereas the 24-hour specimen of urine had shown 210 mg. of ammonia per 100 c.c. (24-hour specimen preserved with toluol). In another case also (No. 100), which showed an increased blood ammonia percentage, as well as an increased ammonia output in the urine, a fresh catheterized specimen of urine from the ureter showed only 13 mg. of ammonia per 100 c.c. as contrasted with a content of the 24-hour specimen of urine, collected according to the usual precautions (toluol) of 330 mg. per 100 c.c.

Two explanations for the differences between the blood ammonia percentages and the ammonia content of the urine in acidosis suggest themselves. One explanation is that the ammonia which is believed to be set free into the blood in order to combine with, and thus neutralize, the excess of acid radicals which are present in acidosis, is set free and excreted in waves, as it were, the patient showing at one time an excess of blood ammonia and at another time showing a normal ammonia content. If this is the case, any excess of ammonia in the blood, whether the ammonia be free or combined, must be excreted by the kidneys, almost as soon as it is produced. Against this theory is the fact that even repeated examinations of the blood of some of our cases of severe acidosis have failed to show any excess at any time. Another explanation for the marked excess of ammonia in the urine in cases of acidosis, with an absence of such excess in the blood, may be, that in acidosis certain bodies are present in the urine which favor a more rapid decomposition of its nitrogenous elements than under normal conditions.

The cause of increased ammonia content of the blood without an acidosis being present presents an interesting question. Three such cases have been observed in this series: case No. 4, in which every test for acidosis was negative, including the hydrogen-ion concentration of the blood; case No. 99, whose alveo-

lar air tension, while slightly lower than normal would not suggest any appreciable degree of acidosis; and case No. 109, showing also only a slightly lowered CO_2 tension. Apparently acidosis as a cause of the ammonia increase can be ruled out in the above cases. An analysis of the cardiorenal cases, showing increased blood ammonia, shows that in addition to the acidosis which was present in all, a condition of chronic passive congestion was also present in all of them, in addition to the acidosis. Moreover, in all of these cases the chronic passive congestion was quite severe. On the other hand, however, a number of cases showing similar chronic passive congestion failed to show an increased blood ammonia percentage. In fact it may be said that the cases of chronic passive congestion showing definite increases of blood ammonia are exceptional, as judged from the cases included in this series, as well as from a number of similar cases studied by us, but not included. A pathologic study of five cardiorenal cases which have come to autopsy and which have shown increased blood ammonia before death, has revealed the typical lesions of marked chronic passive congestion with pressure atrophy about the central veins of the hepatic lobules in each case. The source of the ammonia excess in the blood in the cases of eclampsia studied by us is an interesting subject for speculation. Has it any connection with the hepatic lesions which were shown to be present in at least one of these cases which came to autopsy? Our own series of such cases is too small to determine this point. If it be true, however, that the increase of blood ammonia in such cases may be attributable to the hepatic lesions, a very important differential criterion between hepatic and nephritic toxemia of pregnancy would be offered.

Also in the case of persistent vomiting in a man (case No. 4 of the protocol) in which no evidence of acidosis could be demonstrated in spite of the great increase of blood ammonia, can one explain the clinical symptoms as well as the chemical abnormality of the blood by acute hepatic insufficiency? Certainly his symptoms were similar in many respects to those exhibited by dogs showing evidence of protein intoxication after their livers have been removed from the portal circulation by means of Eck fistulas. Recent work has, however, failed to show any ammonia excess in the blood of such dogs, and Fiske and Karsner have failed in an attempt to produce blood ammonia excess in the blood of animals whose livers have been injured by poison.[11, 14, 15, 16] Also, against disease of the liver as an explanation of blood ammonia increase in these cases, we have studied a series of ten cases of more or less serious disease of the liver, in only one of which, just before death, was any increase of blood ammonia demonstrated. While it is true that an isolated case of marked chronic passive congestion of th liver has occasionally shown an increase in blood ammonia, such cases are, nevertheless, exceptional. Certainly, if ammonia increase in the blood is to be attributed to deficient functional activity of the liver, it must be attributed by a sudden or acute stoppage of the normal function of the cells rather than to either acute or chronic inflammatory diseases of the liver parenchyma as in cirrhosis of the liver, hepatic abscess, etc., in which either compensatory changes must have taken place in the liver or else other organs have been enabled to take up at least a part of its functions.

TABLE I.

CHRONIC DISEASES OF THE LIVER.

SERIAL NUMBER	BLOOD NH_3 (MG. PER 100 C.C.)	URINE NH_3 (MG. PER 100 C.C. AND OUTPUT IN GM. IN 24 HRS.)	BLOOD UREA (MG. PER 100 C.C.)	URINE UREA (OUTPUT IN GM. IN 24 HRS.)	CO_2 TENSION OF ALVEOLAR AIR. (MM. OF HG.)	BICARBONATE TEST. (SELLARD'S TEST.)	ACETONE AND DIACETIC ACID IN URINE	DIAGNOSIS	REMARKS
15	Trace	50 mg. per 100 c.c. (0.49 gm. in 24 hrs.)	46 mg. per 100 c.c.	7.2 gm. in 24 hrs.	37.8 mm.	Positive	None	Laennec's cirrhosis of the liver	Complicated by diarrhea.
45	1.2 mg. per 100 c.c.	45 mg. per 100 c.c. (0.51 gm. in 24 hrs.)	89 mg. per 100 c.c.	5 gm. in 24 hrs.	38 mm.	Negative	None	"	Complicated by chronic diffuse nephritis and ascites.
106	Trace	–	39 mg. per 100 c.c.	–	44 mm.	–	None	"	
82	2.4 mg. per 100 c.c.	60 mg. per 100 c.c. 0.5 gm. in 24 hrs.	328 mg. per 100 c.c.	2.4 gm. in 24 hrs.	34.2 mm.	–	None	"	Complicated by chronic diffuse nephritis and uremia.
84	Trace	–	29 mg. per 100 c.c.	–	41 mm.	Negative	None	"	Complicated by hematemesis.
59	Trace	–	23 mg. per 100 c.c.	–	40.2 mm.	–	–	Syphilitic cirrhosis of the liver	Death in coma. (Autopsy.)
110	Trace	–	26 mg. per 100 c.c.	–	37 mm.	–	–	"	Death from malignant endocarditis. (Autopsy.)
109	6.8 mg. per 100 c.c.	–	22.6 mg. per 100 c.c.	–	38 mm.	Negative	None	"	Blood taken just before death during coma. Death occurred in convulsions.
19	Trace	–	10 mg. per 100 c.c.	–	37.8 mm.	–	+	Carcinoma of head of pancreas	Marked obstructive jaundice. Emaciation marked.
23	Trace	–	15.2 mg. per 100 c.c.	–	47 mm.	–	–	Catarrhal jaundice (acute)	
111	Trace	–	–	–	–	–	–	Amebic abscess of liver	Large amebic abscess.

TABLE II.

DISEASES OF THE HEART.

SERIAL NUMBER	BLOOD NH_3 (MG. PER 100 C.C.)	URINE NH_3 (MG. PER 100 C.C. AND OUTPUT IN GM. IN 24 HRS.)	BLOOD UREA (MG. PER 100 C.C.)	URINE UREA (OUTPUT IN GM. IN 24 HRS.)	CO_2 TENSION OF ALVEOLAR AIR. (MM. OF HG.)	BICARBONATE TEST. (SELLARD'S TEST.)	ACETONE AND DIACETIC ACID IN URINE	DIAGNOSIS	REMARKS
78	Trace	–	35 mg. per 100 c.c.	–	19 mm.	–	None	Myocarditis	Acute dilatation. Marked dyspnea. Chronic passive congestion marked. Autopsy.
14	Trace	30 mg. per 100 c.c. 0.3 gm. in 24 hrs.	65 mg. per 100 c.c.	–	19 mm.	–	+	"	Cheyne-Stokes respiration. Chronic passive congestion marked. (Autopsy.)
24	8.5 mg. per 100 c.c.	40 mg. per 100 c.c. (0.4 gm. in 24 hrs.)	22 mg. per 100 c.c.	6 gm. in 24 hrs.	25 mm.	–	+	Aneurysm, myocarditis	Chronic dilatation. Marked dyspnea. Marked chronic passive congestion. (Autopsy.)
31	Trace	54 mg. per 100 c.c. (0.6 gm. in 24 hrs.)	20 mg. per 100 c.c.	7 gm. in 24 hrs.	39 mm.	–	None	Endocarditis	Aortic insufficiency (compensated partially).
38	Trace	34 mg. per 100 c.c. (0.3 gm. in 24 hrs.)	40 mg. per 100 c.c.	7.5 gm. in 24 hrs.	42 mm.	–	None	"	Compensated valve lesion.
43	Trace	–	38 mg. per 100 c.c.	–	20.5 mm.	–	+	"	Aortic insufficiency. Marked dyspnea. Marked chronic passive congestion.
48	Trace	75 mg. per 100 c.c. (0.32 mg. in 24 hrs.)	23 mg. per 100 c.c.	4 gm. in 24 hrs.	44 mm.	–	None	Myocarditis	
49	Trace	50 mg. per 100 c.c. (0.45 mg. in 24 hrs.)	38 mg. per 100 c.c.	7.2 gm. in 24 hrs.	–	–	None	Endocarditis	Compensated valvular lesion.
50	6 mg. per 100 c.c.	50 mg. per 100 c.c. (0.5 gm. in 24 hrs.)	34 mg. per 100 c.c.	6.5 gm. in 24 hrs.	20 mm.	–	+	Myocarditis	Chronic dilatation. Marked dyspnea. Marked chronic passive congestion.
58	Trace	–	21 mg. per 100 c.c.	–	–	–	+	Myocarditis	Slight dilatation. Dyspnea. Chronic passive congestion.
76	3 mg. per 100 c.c.	–	50 mg. per 100 c.c.	–	22 mm.	–	+	Myocarditis	Chronic dilatation. Marked dyspnea.
35	17 mg. per 100 c.c.	130 mg. per 100 c.c. (1.2 gm. in 24 hrs.)	25 mg. per 100 c.c.	9.5 gm. in 24 hrs.	28 mm.	–	+	Myocarditis	Marked chronic passive congestion. Chronic dilatation. Marked dyspnea. Marked chronic passive congestion. (Autopsy.)
90	3 mg. per 100 c.c.	–	24 mg. per 100 c.c.	–	31 mm.	–	+	Myocarditis	Acute dilatation. Marked chronic passive congestion.
71	4 mg. per 100 c.c.	–	37 mg. per 100 c.c.	–	28 mm.	–	–	Myocarditis	Chronic dilatation. Marked chronic passive congestion. Dyspnea. (Autopsy.)

TABLE III.

ACIDOSIS FROM VARIOUS CAUSES.

SERIAL NUMBER	BLOOD NH_3 (MG. PER 100 C.C.)	URINE NH_3 (MG. PER 100 C.C. AND OUTPUT IN GM. PER 24 HRS.)	BLOOD UREA (MG. PER 100 C.C.)	URINE UREA (OUTPUT IN GM. PER 24 HRS.)	CO_2 TENSION OF ALVEOLAR AIR. (MM. OF HG.)	BICARBONATE TEST. (SELLARD'S TEST.)	ACETONE AND DIACETIC ACID IN URINE	DIAGNOSIS	REMARKS
52	Trace	60 mg. per 100 c.c. (0.48 gm. in 24 hrs.	29.5 mg. per 100 c.c.	9.75 gm. in 24 hrs.	42 mm.	+	++	Diabetes mellitus	Sugar free following starvation.
54	Trace	110 mg. per 100 c.c. (2.5 gm. in 24 hrs.)	–	–	33 mm.	+	++	"	
55	Trace	40 mg. per 100 c.c. (0.78 gm. in 24 hrs.)	29 mg. per 100 c.c.	–	46 mm.	–	Slight amounts	"	
69	Trace	210 mg. per 100 c.c. (5 gm. in 24 hrs.)	22 mg. per 100 c.c.	8.2 gm. in 24 hrs.	18 mm.	++	+++	"	Diabetic coma.
102	Trace	90 mg. per 100 c.c. (1.8 gm. in 24 hrs.)	–	–	32 mm.	–	++	"	
89	Trace	60 mg. per 100 c.c. (0.9 gm. in 24 hrs.)	20 mg. per 100 c.c.	9.6 gm. in 24 hrs.	36.4 mm.	–	++	"	
64	Trace	–	31 mg. per 100 c.c.	–	28 mm.	–	++	Pneumonia	
83	Trace	–	11 mg. per 100 c.c.	–	38 mm.	–	++	Typhoid fever	
65	Trace	–	31 mg. per 100 c.c.	–	24 mm.	–	++	Acute alcoholism (coma)	Alcoholic coma.
79	Trace	–	–	–	30 mm.	–	+++	Postoperative vomiting	Severe vomiting following ether anesthesia.
74	Trace	–	–	–	32 mm.	–	+++	Intestinal obstruction	Intestinal obstruction from adhesions with persistent vomiting.
81	Trace	100 mg. per 100 c.c. (0.4 gm. in 24 hrs.)	26 mg. per 100 c.c.	5.8 gm. in 24 hrs.	28 mm.	–	++	Postoperative vomiting	Persistent vomiting following ether anesthesia.
98	4 mg. per 100 c.c.	–	16 mg. per 100 c.c.	–	24 mm.	–	+++	General peritonitis	Autopsy showed extensive cloudy swelling of all organs and marked fatty degeneration of liver.
100	7 mg. per 100 c.c.	330 mg. per 100 c.c. (1.35 gm. in 24 hrs.)	23 mg. per 100 c.c.	6 gm. in 24 hrs.	29 mm.	–	+++	Persistent vomiting of unknown cause	Chronic (3 weeks) periodic attacks of vomiting. Began following laparotomy for pelvic disease and cholecystitis.

TABLE IV.

NEPHRITIS.

SERIAL NUMBER	BLOOD NH_3 (MG. PER 100 C.C.)	URINE NH_3 (MG. PER 100 C.C. AND OUTPUT IN GM. IN 24 HRS.)	BLOOD UREA (MG. PER 100 C.C.)	URINE UREA (24 HR. OUTPUT IN GM.)	CO_2 TENSION OF ALVEOLAR AIR IN MM. OF HG.	BICARBONATE TEST. (SELLARD'S TEST.)	ACETONE AND DIACETIC ACID IN URINE	DIAGNOSIS	REMARKS
13	6 mg. per 100 c.c.	50 mg. per 100 c.c. (0.52 gm. in 24 hrs.)	140 mg. per 100 c.c.	3.3 gm. in 24 hrs.	30 mm. of Hg.	–	None	Chronic diffuse nephritis (hypertension)	Complicated by dilatation of the heart. Marked chronic passive congestion of liver. (Autopsy.)
17	Trace	–	131 mg.	4 gm. in 24 hrs.	24 mm.	–	None	Chronic diffuse nephritis	Uremia. (Autopsy.)
18	Trace	–	120 mg. per 100 c.c.	2.4 gm. in 24 hrs.	35 mm.	–	None	Chronic diffuse nephritis (hypertension)	
22	4 mg. per 100 c.c.	100 mg. per 100 c.c. (0.8 gm. in 24 hrs.)	20 mg. per 100 c.c.	10.5 gm. in 24 hrs.	32 mm.	–	+	Subacute diffuse nephritis. (Glomerular type)	General anasarca—dilatation of heart. Marked chronic passive congestion of liver. (Autopsy.)
25	3 mg. per 100 c.c.	–	66 mg. per 100 c.c.	7.2 gm. in 24 hrs.	39 mm.	–	None	Chronic diffuse nephritis. (Hypertension)	
26	1.3 mg. per 100 c.c.	–	19.7 mg. per 100 c.c.	–	28 mm.	–	None	Acute diffuse nephritis	General anasarca—dilatation of heart. Chronic passive congestion. Cheyne-Stokes respiration. Recovery.
28	Trace	40 mg. per 100 c.c. (0.4 gm. in 24 hrs.)	38 mg. per 100 c.c.	9 gm. in 24 hrs.	46 mm.	–	None	Chronic diffuse nephritis	
36	Trace	–	95 mg. per 100 c.c.	4.2 gm. in 24 hrs.	40 mm.	–	None	Chronic diffuse nephritis	
37	Trace	44 mg. per 100 c.c. (0.5 in 24 hrs.)	58 mg. per 100 c.c.	6 gm. in 24 hrs.	38 mm.	–	None	Chronic diffuse nephritis	Marked dyspnea. Chronic passive congestion marked. Death. (Autopsy.)
39	Trace	–	253 mg. per 100 c.c.	–	32 mm.	–	None	Chronic diffuse nephritis	Uremia. Death.
42	Trace	–	40 mg. per 100 c.c.	10 gm. in 24 hrs.	49 mm.	–	None	"	Anasarca.
44	1.2 mg. per 100 c.c.	–	25 mg. per 100 c.c.	–	47 mm.	–	None	"	
47	Trace	90 mg. per 100 c.c. (0.6 gm. in 24 hrs.)	110 mg. per 100 c.c.	8.4 gm. in 24 hrs.	34 mm.	–	+	"	Dyspnea marked. Marked chronic passive congestion of liver.
51	1 mg. per 100 c.c.	–	236 mg. per 100 c.c.		15.5 mm.		None	Chronic diffuse nephritis	Uremia. (Autopsy.)
57	Trace	–	34 mg. per 100 c.c.		42 mm.		None	"	
68	Trace	48 mg. per 100 c.c. (0.8 gm. in 24 hrs.)	80 mg. per 100 c.c.	9.2 gm. in 24 hrs.	–	–	None	"	
80	9 mg. per 100 c.c.	93 mg. per 100 c.c. (0.75 gm. in 24 hrs.)	128 mg. per 100 c.c.	2.8 gm. in 24 hrs.	28 mm.	–	None	"	Dyspnea marked. Chronic passive congestion marked. Death. Uremic coma. (Autopsy.)
82	Trace	60 mg. per 100 c.c. (0.5 gm. in 24 hrs.)	328 mg. per 100 c.c.	4.8 gm. in 24 hrs.	34.2 mm.	–	None	"	Cheyne-Stokes respiration. Uremia. (Autopsy.)
86	Trace	–	71 mg. per 100 c.c.	9.6 gm. in 24 hrs.	–	–	None	"	

TABLE V.

A CASE OF PERSISTENT PERIODIC VOMITING OF UNKNOWN ETIOLOGY.

SERIAL NUMBER	BLOOD NH_3 (MG. PER 100 C.C.)	URINE NH_3 (MG. PER 100 C.C. AND OUTPUT IN GMS. PER 24 HRS.)	BLOOD UREA (MG. PER 100 C.C.)	URINE UREA OUTPUT IN GM. PER 24 HRS.	CO_2 TENSION OF ALVEOLAR AIR. (MM. OF HG.)	BICARBONATE TEST. (SELLARD'S TEST.)	H-ION CONCENTRATION OF BLOOD	ACETONE AND DIACETIC ACID IN URINE	REMARKS
4 10/26/16	23 mg. per 100 c.c.	80 mg. per 100 c.c. or 0.9 gm. per 24 hrs.	36 mg. per 100 c.c.	13.6 gm. in 24 hrs.	45 mm.	Negative	pH 8.4 (Marriott's Method)	None	Persistent (4 weeks) periodic vomiting attacks in a chronic alcoholic. Patient toxic and very drowsy, but irritable and querulous when disturbed. Complains of weakness in left leg.
4 11/3/16	17 mg. per 100 c.c.	–	–	–	43 mm.	"		"	
4 11/22/16	12 mg. per 100 c.c.	–	–	–	45 mm.			"	
4 12/3/16	8 mg. per 100 c.c.	–	–	–	46 mm.				No vomiting. Nausea only.
4 12/14/16	Trace	40 mg. per 100 c.c. (0.4 gm. per 24 hrs.)	–	–	45 mm.			"	Vomiting and toxemia have disappeared. No nausea.
4 12/28/16	3 mg. per 100 c.c.	–	–	–				"	Specimen taken following a recurrence of nausea and vomiting.
4 1/2/17	Trace	–	–	–				"	

TABLE VI.

TOXEMIAS OF PREGNANCY.

SERIAL NUMBER	BLOOD NH_3 (MG. PER 100 C.C.)	URINE NH_3 (MG. PER 100 C.C. AND OUTPUT IN GM. PER 24 HRS.)	BLOOD UREA (MG. PER 100 C.C.)	URINE UREA (OUTPUT IN GM. PER 24 HRS.)	CO_2 TENSION OF ALVEOLAR AIR. (MM. OF HG.)	BICARBONATE TEST. (SELLARD'S TEST.)	ACETONE AND DIACETIC ACID IN URINE	DIAGNOSIS	REMARKS
77	Trace	–	68 mg. per 100 c.c.	–	–	–	+	Nephritic toxemia of pregnancy	Sudden onset with convulsions toward latter end of pregnancy. Albumin blood and casts in urine.
105	10.2 mg. per 100 c.c.	–	25 mg. per 100 c.c.	–	–	–	++	Eclampsia	Sudden onset with convulsions toward termination of pregnancy. Albumin and casts in urine. Autopsy showed typical hepatic focal necroses of eclampsia.
99	7 mg. per 100 c.c.	–	27 mg. per 100 c.c.	–	38 mm.	Negative	None	Eclampsia (?)	Postpartum convulsions. Recovery.
91	3.4 mg. per 100 c.c.	110 mg. per 100 c.c. (1.5 gm. per 24 hrs.	20 mg. per 100 c.c.	8.9 gm. per 24 hrs.	28 mm.	–	++	Vomiting of pregnancy	Persistent vomiting early in pregnancy. Recovery.

CONCLUSIONS.

1. Increases of blood ammonia of above 1 mg. per 100 c.c. are occasionally met with in various diseases.

2. Such increases can not be explained by acidosis in all cases.

3. The fact that nine cases showing marked increases (over 3 mg. per 100 c.c.), which have come to autopsy, have shown definite hepatic lesions would suggest some connection between increased blood ammonia and functional insufficiency of the liver.

4. The fact that of ten chronic and subacute cases of inflammatory disease of the liver studied, only one has shown an increase of blood ammonia would indicate acute functional insufficiency of the liver cells rather than acute or chronic inflammatory changes in the liver parenchyma as the source of any blood ammonia increase.

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INFECTIOUS MENINGITIS—A STUDY OF 27 CASES IN 586 AUTOPSIES*

By Stuart Graves, M.D., Louisville, Ky.

OF 586 autopsies done in the pathologic laboratory of the Medical Department of the University of Louisville and of the Louisville City Hospital between September 1, 1914, and April 1, 1917, 27 revealed leptomeningitis, a percentage of 4.6. From a study of this material it is my purpose to present some statistics and conclusions of interest and value particularly to the clinician. It must be borne in mind that some of these subjects were coroner's cases which had been sent into the laboratory for autopsy and had not been on the wards at all; some were practically moribund when admitted to the wards; and some, it must be confessed, did not come to autopsy with as complete and accurate records as could be desired. The cases examined were briefly as follows:

ABBREVIATED PROTOCOLS OF THE CASES.

(1) A-14-3. Adult, male, white, age unknown. Coroner's case.

Excerpt from chart: Admitted Sept. 12; provisional diagnosis, septic meningitis. Died that afternoon. Temperature 99.1°; pulse 126; respiration 28. Patient irrational on admission. Six days before, while working in a stable, had become irrational. Three days later condition became so aggravated that he was dismissed from work. Gradually developed coma, in which condition he was brought to hospital with psychomotor unrest, retraction of eyes, contracted pupils, positive Kernig. Lumbar puncture showed bacillus mucosus capsulatus.

Autopsy findings: Piarachnoid of cerebrum, cerebellum and cord covered with a thick, yellow, mucoid exudate. Smears and cultures showed Gram-negative, encapsulated bacilli, gas, acidified milk and thick, mucoid growth on agar. Bacteriologic diagnosis, bacillus mucosus capsulatus. Lungs and middle ears negative.

(2) A-14-11. Negro, female, 8 months old.

Excerpt from chart: Admitted Sept. 24; died Oct. 4. Clinical diagnosis, tuberculous meningitis. Uncle living in house during first four months of child's life had tuberculosis. Last four months patient had cough, spasms with vomiting and later crepitant and moist rales over right apex. Spinal fluid: No organisms found, moderate increase in lymphocytes. Temperature 98.6° to 103.4°; pulse 130 to 154; respirations 26 to 64.

Autopsy findings: General miliary tuberculosis of lungs, liver, spleen, kidneys, ileum and meninges of brain and cord. Grayish exudate along left middle cerebral vessels, beginning over right Sylvian fissure and extending chiefly over base of cerebrum around circle of Willis. Scattered miliary tubercles also found. Cord not removed.

(3) A-14-16. Negro girl 16 years old. Coroner's case.

Excerpt from chart: Admitted Oct. 12; died Oct. 16. No history obtainable because of condition of patient. No neck rigidity present afternoon before death. Spinal fluid showed 723 polymorphonuclear leucocytes per cubic millimeter; coagulated in heating for globulin test. No Kernig obtainable. Whilte count, 6,200; polymorphonuclear leucocytes, 66%. Temperature 98.4° to 101°; pulse 92; respirations 28.

Autopsy findings: Pulmonary tuberculosis. Miliary tuberculosis of spleen, liver and kidneys. Piarachnoid grayish and slightly thickened along middle cerebral arteries, but no frank exudate. Similar condition in upper portion of cord. Sections showed tuberculous meningitis of cerebrum and cord.

(4) A-14-27. White, male, 23 years old. Coroner's case.

Excerpt from chart: Patient had been thrown from motorcycle on Sept. 17, 1914,

*From the Pathologic Laboratory of the Medical Department of the University of Louisville and of the Louisville City Hospital.
Read before the Jefferson County Medical Society, May 21, 1917.

and sustained fracture of frontal bone. X-ray showed fracture of left frontal bone extending from outer angle of left eye upward and across median line. Ran irregular temperature from 97.4° to 100.4°. Discharged Oct. 15 with normal temperature, pulse and respirations. Readmitted Oct. 23 and trephined Oct. 26. Died that afternoon. No symptoms recorded. Temperature 98° to 104°; pulse 120.2; respirations 22. Lumbar puncture day of admission showed 2070 cells per cubic millimeter; 98% polymorphonuclear leucocytes. Lumbar puncture two days later showed 1330 cells per cubic millimeter; 83% polymorphonuclear leucocytes. Smears and cultures showed pneumococci.

Autopsy findings: Entire surface of piarachnoid of brain and cord covered with a grayish white exudate. Sections showed acute leptomeningitis.

(5) A-14-42. Negro, female, adult, age 59 years.

Excerpt from chart: Admitted Nov. 3; died Nov. 6. Complained of pain in head, neck, chest and back. No antemortem diagnosis, lumbar puncture, physical examination or blood count recorded. Temperature subnormal until last day when it rose to 103°; pulse 78; respirations 24.

Autopsy findings: On right side of longitudinal fissure piarachnoid opaque and yellow, most marked along course of vessels. Similar condition along middle cerebral arteries, more marked over base of brain. Smears from exudate showed pus cells and Gram-positive, lancet-shaped diplococci, morphologically pneumococci.

(6) A-14-55. Negro, female, adult.

Excerpt from chart: Admitted Nov. 25; died at 3 P.M. Provisional diagnosis: Cerebral hemorrhage.

Autopsy findings: Lobular pneumonia, meningitis. Small localized areas of grayish exudate over surface of brain, most marked along margin of cerebellum. Cord grossly negative. Smears from cerebellum showed Gram-positive, encapsulated diplococci, morphologically pneumococci.

(7) A-14-73. Coroner's case outside. Negro, female, adult. No history.

Autopsy findings: Entire surface of piarachnoid of cerebrum, cerebellum, and cord covered with thick, yellow, purulent material, especially along vessels. Middle ears negative. Smears showed many pus cells and Gram-negative, biscuit-shaped, intra- and extracellular diplococci, morphologically meningococci.

(8) A-15-20. Negro, male, adult.

Excerpt from chart: Patient admitted Jan. 28, at noon; died at 9 P.M. Admitted unconscious. No history or physical examination on chart. Temperature 101.6° (axillary); pulse 140; respirations 48.

Autopsy findings: Lobular pneumonia. Along vessels of pia mater of the dorsum of the brain were seen yellowish, opaque stripes. Over frontal lobes there was a thick, dense, opaque, yellowish material beneath pia entirely concealing the vessels and brain tissue. This thick, dense, opaque, yellowish material found beneath pia in region of pons, medulla, and under surface of temporal lobes. Beneath pia of spinal cord were seen yellowish areas varying from 1 to 4 mm. in diameter, scattered throughout its entire length. Smears showed pus cells and Gram-positive diplococci, encapsulated, morphologically pneumococci.

(9) A-15-33. Negro, male, adult.

Excerpt from chart: Admitted March 6; died March 9. Patient delirious; no history obtainable. Neck stiff. Kernig positive. Spinal puncture showed white blood cells, 186; polymorphonuclear leucocytes, 68%; lymphocytes, 32% (Blood?). No tubercle bacilli found. Blood count, March 6; W. B. C., 10,600; polymorphonuclear leucocytes, 80%; R. B. C., 2,500,000. Temperature 100° to 102.4°; pulse extremely irregular, 60 to 150 with daily change; respirations 20 to 40.

Autopsy findings: About poles of temporal lobes, pons, and optic chiasm piarachnoid showed grayish yellow, thick exudate along vessels. Cord showed occasional yellowish gray, rounded nodules 1 mm. in diameter. Smears from meninges of brain and cord showed numerous lymphocytes and tubercle bacilli. Sections showed miliary tuberculosis of lungs, spleen and liver and conglomerate tuberculosis of adrenals. Middle ears, negative.

(10) A-15-45. Negro, male, 58 years old.

Excerpt from chart: Admitted March 13; died April 6. History of two attacks of rheumatism, last one six years ago. Clinical signs and symptoms showed consolidation of base of upper lobe on left side. White count just before death showed 1500 leucocytes.

Autopsy findings: Vegetative endocarditis. Infarct of left lung. Cerebrospinal meningitis. Piarachnoid over medulla, pons, and cerebellum and inferior surfaces of frontal and temporal lobes presented a dense, opaque, grayish yellow exudate, 2 to 3 mm.

thick. Similar exudate over entire spinal cord. Smears from meninges showed Gram-positive, encapsulated, lancet-shaped diplococci, intra- and extra-cellular, with cultural characteristics of pneumococci.

(11) A-15-53. Male, negro, 66 years old.

Excerpt from chart: Admitted March 19; died April 19. No diagnosis recorded. Temperature ranged between 97 and 100; pulse 72 to 98; respirations 20 to 30.

Autopsy findings: Cerebral leptomeningitis. Infarct of right lung. Piaarachnoid showed grayish white streaks along vessels near vertex and over parietal lobe and posterior portion of frontal lobe on either side. Smear from meninges showed Gram-positive, spherical cocci in short chains up to eight units, morphologically streptococci. Middle ear, negative.

(12) A-15-57. Negro, male, adult.

Excerpt from chart: Admitted Jan. 21; died April 29. Suprapubic cystotomy done immediately after admission to relieve complete anuria and greatly distended bladder, urethra being occluded with stricture. Patient improved daily until day before death when he had two convulsions and ceased to breath. Temperature irregular, 96.4° to 103°; pulse 90 to 120; respirations 18 to 38.

Autopsy findings: Lobar pneumonia. Obliterative pleural and pericardial fibrous adhesions. Acute tubular nephritis. Cerebral leptomeningitis. There was a narrow, dense, grayish white opacity along vessels of both hemispheres on either side of fissure of Rolando, extending 3 to 4 cm., being more prominent near vertex. Smears and cultures from heart's blood and meninges (11 hrs. postmortem) showed morphologic and cultural characteristics of pneumococci.

(13) A-15-58. Negro, male, 45 years old.

Excerpt from chart: Admitted April 28 unconscious; died April 30. Provisional diagnosis: Cerebral hemorrhage. White count, 10,000; polymorphonuclear leucocytes, 72%. Lungs: Some mucous rales present; no dullness.

Autopsy findings: Lobar pneumonia. Chronic myocarditis. Cerebral leptomeningitis. On either side of vessels in region of Rolandic fissure were grayish white, opaque streaks, more marked in upper portion. Smears showed Gram-positive, lancet-shaped diplococci, morphologically pneumococci.

(14) A-15-78. Female, negro, adult.

Excerpt from chart: Admitted May 20 and died almost immediately. Unconscious. Had been sick three weeks with frequent convulsions day and night for three days before admission. Mucous rales present posteriorly over both lungs. Temperature 99°; pulse 120; respirations 32. No Wassermann done.

Autopsy findings: Lobular pneumonia. Healing pericarditis. Chronic internal hemorrhagic pachymeningitis. Sections showed also chronic leptomeningitis. Bacteriology of meninges not studied.

(15) A-15-171. White, male, 14 years old.

Excerpt from chart: Admitted Sept. 26; died Oct. 24. Discharging ear for six years. Three weeks before admission began to have pain behind left ear. Physical examination revealed tenderness over left mastoid. Mastoidotomy done. Temperature on admission, 101°, continued irregular, 97.4° to 105.2°; pulse 74 to 144, rising to 168 in last three days; respirations 24 to 36 in last three days. No antemortem bacteriology. Clinical diagnosis: Otitis media. Mastoiditis. Secondary meningitis.

Autopsy findings: Acute leptomeningitis and otitis media, left side. Left antrum chiseled out and clean. Smears from left middle ear and base of brain showed pus cells and few Gram-positive diplococci, spherical, in short chains up to six units. Organisms did not grow on culture. Diagnosis, morphologically streptococci.

(16) A-15-217. Negro, female, 26 years old.

Excerpt from chart: Admitted on Dec. 31; died immediately after admission. Provisional diagnosis, meningitis. Temperature 101.8°; pulse 110; respirations 28. No laboratory findings recorded.

Autopsy findings: Acute cerebral leptomeningitis. Narrow, grayish yellow streaks along vessels of cortex in region of Rolandic fissure. These streaks faded out before reaching base of brain. Smears showed Gram-negative, extracellular, biscuit-shaped diplococci.

(17) A-16-11. Negro, female, 48 years old.

Excerpt from chart: Admitted Dec. 31; died Jan. 8. Final diagnosis: Lobar pneumonia. Physical examination showed slight jaundice. Temperature day before death, 103°; pulse, 110; respirations, 42.

Autopsy findings: Acute endocarditis. Lobular pneumonia with sections showing

acute arteritis. Healing leptomeningitis. Smears and cultures from heart's blood, valvular vegetations along tricuspid valve and from meninges all showed hemolytic streptococci. Middle ears negative. In piarachnoid and convolutions about cortex of cerebrum were a few pinhead, grayish white areas. Pyorrhea alveolaris marked.

(18) A-16-115. Negro, female, 8 years old.

Excerpt from chart: Admitted May 21; died next day. Diagnosis: Tuberculous meningitis. Child had been sick since Thanksgiving. Began vomiting all food taken. Had had high temperature since beginning of trouble. Brought in in dying condition. Emaciated and anemic. Few rales in both apices; bases dull. Legs spastic. Kernig present. In opisthotonos and unconscious condition before death. At midnight convulsions every few minutes. Temperature (axillary), 104.6°; pulse 144; respirations 56.

Autopsy findings: Miliary tuberculosis of lungs, spleen, stomach, pancreas, liver, kidneys, cerebrum, cerebellum, and cord. Piaarachnoid over base of cerebrum showed increase in clear watery fluid. Grayish yellow exudate along vessels near Sylvian fissure and over base. Similar exudate over cerebellum with numerous scattered, pinhead areas. Left caudate nucleus showed marked softening in area 2 cm. in diameter which extends to anterior limb of internal capsule. This area was pinkish yellow, soft and mushy. Sections showed tuberculosis. Smears showed tubercle bacilli.

(19) A-16-117. Negro, male, 35 years old.

Excerpt from chart: Admitted May 26; died May 26. Diagnosis: Edema and congestion of lungs. Illness began three days before admission with chill and pain in back of head. This was followed by repeated convulsions. Physical examination showed moist rales over both lungs. Leucocytic count, 9,400; polymorphonuclear leucocytes, 74%. Urine showed albumin. Temperature 105.7°; pulse 140; respirations 40.

Autopsy findings: Meninges of medulla, pons and base of brain showed grayish yellow, opaque streaks along vessels. Lateral, third and fourth ventricles filled with thin, grayish yellow, purulent material. Middle ears negative. Smears from meninges showed Gram-negative, intra- and extra-cellular, biscuit-shaped diplococci. Smears from fluid in lateral ventricles showed same. Microscopical sections showed lobular pneumonia, infarct of spleen, beginning glomerular nephritis and regeneration of adrenal cortex with numerous mitotic figures.

(20) A-16-122. Negro, male, 32 years old.

Excerpt from chart: Admitted and died on June 4. Patient had been struck on head by automobile three days before. Morning of admission had become delirious and violent.

Autopsy findings: Fracture of base of skull involving left petrous portion of left temporal bone. Acute leptomeningitis. Suppurative otitis media. Smears and cultures of meninges and middle ear showed pneumococci. Temperature (axillary), 103.8°; pulse 86; respirations 36.

(21) A-16-138. Coroner's case outside. Negro, female, adult. No history.

Autopsy findings: Generalized tuberculosis. Tuberculous leptomeningitis. Tuberculosis of choroid plexus. Choroid plexus on either side showed grayish white, multiple, pinhead areas; on section grayish yellow and soft. Sections showed tuberculosis. Smear from meninges showed tubercle bacilli.

(22) A-16-139. Coroner's case outside. No history. Male negro, 24 years old. Body restricted.

Autopsy findings: Stellate fracture of base of skull. Acute otitis media, right. Sections showing acute cerebral leptomeningitis extending into cerebral cortex. Smears and cultures from meninges and middle ear showed pneumococci.

(23) A-16-159. Female, negro, 17 years old.

Excerpt from chart: Admitted Aug. 6; died Aug. 8. Final diagnosis, tuberculous meningitis. Physical examination showed slight rigidity of spine. All reflexes absent. No sensation below waist. Spinal fluid yellowish and syrupy (Froin's syndrome). Butyric acid test, positive. Temperature 100° to 107°; pulse 124 to 140; respirations 24 to 42. Urine showed albumin. White count 11,600.

Autopsy findings: Body restricted. Sections of brain and cord showed tuberculous meningitis.

(24) A-16-169. White, male, 52 years old.

Excerpt from chart: Admitted Aug. 22; died Aug. 30. Patient admitted semiconscious. Complained of ear trouble. Three days before death had general convulsions. Neck rigid. Kernig positive on both sides. Spinal puncture showed pus cells and a few Gram-positive diplococci; cultures negative after nine days. Leucocytic count, 14,600 to 25,900. Urine showed albumin. Mastoid operation done.

Autopsy findings: Organizing leptomeningitis of brain and cord. Right middle ear negative; left showed mastoidotomy wound and was filled with blood clot. Bacteriology (1 hour postmortem) showed streptococci and staphylococcus aureus of meninges of cerebrum, cord and left middle ear.

(25) A-16-227. White, male, 52 years old.

Excerpt from chart: Admitted Dec. 26; died Dec. 29. Diagnosis, otitis media, cerebrospinal meningitis, pneumococcic. Patient had been admitted to hospital on Nov. 26 and discharged on Dec. 16. Had been admitted for pain and discharge in right ear and paracentesis had been done. Had no temperature or other symptoms when discharged. Readmitted on Dec. 26 with severe pain in right parietal and temporal regions. He staggered when walked and became delirious. On Dec. 27 he became unconscious. Spinal puncture showed pneumococci. Right side of face paralyzed. Marked tenderness over mastoid. Neck rigid. Kernig positive in both legs. Hyperesthesia marked. Temperature varied from subnormal to 102.6°; pulse 82 to 132, rising before death; respirations mostly 20 to 26, rising to 40 before death.

Autopsy findings: Acute purulent otitis media. Mastoiditis Labyrinthitis. Acute diffuse fibrino-purulent cerebral leptomeningitis. Lobar pneumonia. Beginning central necrosis of liver. Acute glomerular and tubular nephritis. Toxic adrenalitis with regeneration (mitoses numerous in cortex). Smears and cultures from heart's blood, cerebral meninges and right fossa over middle ear showed pneumococci.

(26) A-17-1. Negro, female, 40 years old.

Excerpt from chart: Admitted Jan. 5; died Jan. 9. Diagnosis, meningitis. Unconscious when admitted, remained unconscious to death. At times had a muttering delirium. Some exophthalmos. Pupils slightly dilated and did not react to light. Reflexes exaggerated. Babinski, positive. Incontinence of urine and feces. Spinal fluid clear; pressure not increased; apparently no cell count made. Another specimen of spinal fluid showed Wassermann positive +++. Temperature showed daily rise, 99° to 104.6°; pulse 88 to 124; respirations 22 to 44.

Autopsy findings: Lobar pneumonia. Gumma of calvarium, meninges and cerebrum. Healing cutaneous syphilides. Syphilitic deformity of nose. Chronic valvular and mural endocarditis. Postmortem Wassermann positive +++.

(27) A-17-11. Negro, female, 31 years old.

Excerpt from chart: Admitted Jan. 12; died Jan. 23. Provisional diagnosis, multiple bruises and lacerations of right leg. Final diagnosis, tetanus. Eight days after admission patient complained of stiffness of jaws and slight sore throat. Five thousand units of antitetanic serum given subcutaneously and an equal dose given intravenously. Two days later 5,000 more given intraspinously; the following day 6,000 intravenously and 3,000 subcutaneously. That day had slight convulsion of shoulders and head. Patient semiconscious and unable to sleep. Neck and back arched and stiff. More convulsions with rigidity of neck and spine. Frequent chronic convulsions followed with profuse diaphoresis day before death. During last hours lay in stupor. Temperature rose to 100° day of admission and continued with irregular rises as high as 102.4°. Pulse varied daily between 64 and 100, rising to 166 day before death and 106 on day of death. Respirations mostly 20 to 30, rising to 60 day before death. No laboratory examinations recorded.

Autopsy findings: Piarachnoidal space over hemispheres contained a slight excess of clear, watery fluid. Vessels distended. In sulci along left Sylvian fissure piarachnoid contained a milky fluid, more marked along vessels. Left middle ear contained a brownish yellow tenacious fluid. Postmortem bacteriology: Smear from left middle ear showed Gram-positive, discrete, lancet-shaped diplococci, morphologically pneumococci. Smear from left cerebral hemisphere showed many polymorphonuclear leucocytes, some lymphocytes and a few discrete diplococci, morphologically pneumococci. On culture a few Gram-positive diplococci were found, but the growth, in spite of sterile precautions in taking culture, was overgrown with a Gram-positive, irregular diphtheroid. Postmortem diagnoses: Healing otitis media, left. Healing leptomeningitis.

INFECTIOUS AGENTS AND ROUTES OF ENTRANCE.

In the treatment of meningitis, as well as in its prognosis, it is of the utmost importance to ascertain its causative factor. In this series the infectious agents were divided as follows:

Pneumococcus, 11 cases, 40.7%;

Tubercle bacillus, 6 cases, 22.2%;

Meningococcus, 3 cases, 11.1%;
Streptococcus, 3 cases, 11.1%;
Bacillus mucosus capsulatus, 1 case, 3.7%;
Staphylococcus aureus and streptococcus combined, 1 case, 3.7%;
Treponema pallida, 1 case, 3.7%;
Undetermined, 1 case, 3.7%.

It is important also to consider the probable route of entrance of the infection to the meninges and the associated infectious lesions. As nearly as can be ascertained in these cases those factors are shown in Table I.

TABLE I.

ROUTE OF ENTRANCE	NUMBER	PER CENT	PROBABLE SOURCE
Traumatic	3	11.1	Fracture of frontal bone, 1 Fracture of temporal bone, 1 Fracture of base of skull, 1
Hematogenous	14	51.8	Lungs, 6 Generalized tuberculosis, 5 Acute endocarditis, 2 Syphilis, 1
Direct extension	7	25.9	Otitis media, 4 Nares (meningococcus), 3
Undetermined	3	11.1	
(Tuberculosis, body restricted, 1)			
(Chronic internal hemorrhagic pachymeningitis, 1)			
(Unknown, 1)			

Statistics as to age, sex and race are of no particular value if they are not figured in proportion to all patients admitted. The youngest patient was eight months old and the oldest sixty-six years. On the charts of many of the patients the exact age was not stated. However, figuring babes 1 to 5 years old, children 5 to 20, and adults more than 20, the statistics are as follows:

STATISTICS AS TO AGE.

Babes,	1	4%
Children,	4	14%
Adults,	22	82%

RACE AND COLOR.

	Black	Per cent	White	Per cent	Total	Per cent
Male	9	33.3	5	18.4	14	51.7
Female	12	44.4	1	3.7	13	48.1
Total	21	77.7	6	22.1	27	99.8

INJURY AND REACTION.

The injury was severe, with more or less extensive necrosis and acute inflammatory reaction, in the infections due to bacillus mucosus capsulatus, pneumococcus, meningococcus and streptococcus and staphylococcus aureus; less severe, with more localized tissue destruction and chronic inflammation in infections due to tubercle bacilli and treponema pallida and in chronic internal hemorrhagic pachymeningitis, although in only one case, that of a negro baby, was the tuberculous injury and reaction limited to miliary tubercles in the piarachnoid.

TABLE II.

LUMBAR PUNCTURE AND DIAGNOSIS.

CASE NUMBER.	MENINGITIS DIAGNOSED ANTEMORTEM	MENINGITIS DIAGNOSED POSTMORTEM	LUMBAR PUNCTURE DONE ANTEMORTEM
1	Yes	Yes	Yes
2	Yes	Yes	Yes
3	Yes	Yes (Tuberculous)	Yes[1]
4	Yes	Yes	Yes
5	No	Yes	No
6	No (Cerebral hemorrhage)	Yes	No
7	No	Yes	No[2]
8	No	Yes	No
9	Yes	Yes (Tuberculous)	Yes[1]
10	No	Yes	No
11	No	Yes	No
12	No	Yes	No
13	No (Cerebral hemorrhage)	Yes	No
14	No	Yes (Chronic internal hemorrhagic pachymeningitis)	No
15	Yes	Yes	No[3]
16	Yes	Yes	No[3]
17	No	Yes	No
18	Yes	Yes	No[3]
19	No	Yes	No[4]
20	No	Yes	No
21	No	Yes	No[2]
22	No	Yes	No[2]
23	Yes	Yes	Yes
24	Yes	Yes	Yes
25	Yes	Yes	Yes
26	Yes	Yes	Yes[5]
27	No	Yes	No

[1]Cases 3 and 9 were not diagnosed tuberculous meningitis antemortem apparently because all the spinal fluid was collected in one tube in each case. In the first case, the chart states, the spinal fluid contained "723 polymorphonuclear leucocytes per cubic millimeter and coagulated in heating for globulin test;" in the second case, "186 leucocytes per cubic millimeter, polymorphonuclear leucocytes 68%, lymphocytes 32%."

[2]Cases 7, 21, and 22 were not ward cases, but coroner's cases sent in for diagnosis without any clinical history.

[3]In these cases the antemortem diagnosis was obvious from the clinical condition. In the first there was a complicated mastoidotomy. In the second the diagnosis was made in the admission room. In the third marked signs of systemic tuberculosis were present in a negro girl of eight with positive Kernig and opisthotonos.

[4]The infecting organism in each case was proved at autopsy to be meningococcus. Case 7 was an outside coroner's case. Case 16 died immediately after admission. Case 19 was in the ward less than one day.

[5]Wassermann on spinal fluid antemortem and on blood postmortem (3 hrs.) positive +++.

As is well known, the tubercle bacilli, once they gain access to the loose tissues of the meninges, may excite a more or less diffuse and acute inflammatory reaction. As to termination, all inflammatory reactions end in resolution or organization. In only two types of these cases was there evidence of organization, in the luetic and tuberculous. None came to complete resolution, although, as we shall show, at least three might have done so if they had been properly diagnosed and treated. No serious complications of organization were found.

THE SIGNS AND SYMPTOMS.

Of the signs and symptoms recorded in these cases the most common and striking include the following: (1) *Fever.* The temperature was elevated in

every case except one in which it was subnormal until the day of death when it rose to 103° F. The highest temperature was in tuberculous meningitis in which it was recorded at 107° F., although it reached 105.7° F. in a meningococcus infection, and 105.2° F. in a streptococcus infection; (2) *headache;* (3) *rigidity of neck and back;* (4) *Kernig;* (5) *contracted or dilated and fixed pupils;* (6) *vomiting;* (7) *motor reaction to cortical irritation;* (8) *delirium;* (9) *coma;* (10) *hyperesthesia;* (11) *pathologic spinal fluid.*

Osler says in his textbook on medicine that convulsions "are less common in simple than in tuberculous meningitis and that they were not present in a single instance in the cases which I have seen in pneumonia, ulcerative endocarditis or septicemia."

In this series convulsions are recorded in one case of lobar pneumonia and pneumococcus septicemia, in two of lobular pneumonia and healing pericarditis, in one case of complicated mastoiditis, in one of complicated otitis media and in only one of tuberculosis. Rigidity of the neck is not always present. In one case of tuberculous meningitis the chart stated positively that it was not present the afternoon before death.

The most important lesson to be drawn from this study concerns lumbar puncture and spinal fluid. Table II illustrates graphically the relation of antemortem and postmortem diagnoses and the presence or absence of an antemortem spinal puncture.

From the preceding table it can be deduced that correct antemortem diagnoses were made in 10 of 27 cases (1, 2, 4, 15, 16, 18, 23, 24, 25, 26) and that in these cases proper lumbar punctures and spinal fluid examinations were made in 8, while in 17 of 27 cases (3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 17, 19, 20, 21, 22, 27) correct antemortem diagnoses were not made and in such cases a lumbar puncture was not made in a single case.

CONCLUSIONS.

The conclusions are obvious:

1. Correct antemortem diagnoses were established in 100% of cases in which proper lumbar punctures and spinal fluid examinations were made.

2. Correct antemortem diagnoses were not established in 70% of cases in which proper lumbar punctures and spinal fluid examinations were neglected.

3. In drawing spinal fluid the second portion should always be collected in a separate, clean, dry, sterilized test tube. Any blood in the specimen to be examined renders findings unreliable, wastes time and material and may lead to incorrect conclusions.

4. A grave responsibility rests upon the doctor who neglects to have made a proper lumbar puncture and a correct examination of the spinal fluid in all cases of possible meningitis, because the establishment of an early diagnosis and the employment of specific treatment with Flexner's antimeningococcus serum are likely to save lives in meningococcus meningitis at least. The neglect of such measures, conversely, may result in unwarranted fatalities.

I take pleasure in acknowledging careful routine work in the autopsies during the period of this study by members of the laboratory staff, Drs. A. H. Stein, J. W. Moore, H. E. Fust, H. H. Reeder, H. R. Livesay, and T. R. Maxwell.

THE PREVENTION OF SIMPLE GOITER IN MAN*

A Survey of the Incidence and Types of Thyroid Enlargements in the Schoolgirls of Akron (Ohio), from the 5th to the 12th Grades, Inclusive—The Plan of Prevention Proposed.

By David Marine, M.D., and O. P. Kimball, B.S., Cleveland, Ohio.

SIMPLE goiter in animals is probably the easiest of all known diseases to prevent. Simple goiter includes all the thyroid enlargements seen in the lower animals and those thyroid enlargements seen in man, except cases properly classified as exophthalmic goiter. Many cases with simple goiter later develop exophthalmic goiter. In brief, simple goiter includes all those thyroid enlargements formerly classified as endemic, epidemic and sporadic. The periods when it most frequently develops are (1) fetal, (2) adolescent, and (3) during pregnancy. Anatomically a wide range of changes may be present, depending on the species of animal and on the stage (duration) of the disease. In man and fowls one more commonly sees the form characterized by an abundance of colloid material—the so-called "cystic or colloid goiter" of older writers, while in goiter of dogs, sheep, cattle, pigs, fish, etc., the accumulation of colloid material is seen only in the late, regressive or quiescent stages. Again in man the adenomatous form is very common and is exceedingly rare if present at all in the lower animals.

It will not be possible to review all the experimental data on which the assertion, that simple goiter in animals is an easily preventable disease, is based. Certain of the more important facts bearing on the subject will be summarized as an introduction to the discussion of the means proposed to attempt the prevention of simple goiter in man.

1. The developmental stage of all goiters is characterized by an increased blood flow, an increase in the size and number of epithelial cells, a decrease in the stainable colloid of the follicular spaces and a marked absolute decrease in the iodine content. The decrease in iodine precedes the cellular changes.

2. Similar thyroid changes (compensatory hyperplasia) invariably occur in the remaining portion of the gland when a sufficient portion of the entire gland is removed. The amount of gland it is necessary to remove in order to cause compensatory hyperplasia varies somewhat with the species of animal, definitely with the age, the diet, and the presence of iodine.

3. The administration of exceedingly small amounts of any salt of iodine thus far tried in any manner completely protects the remaining thyroid against compensatory hyperplasia, even after the removal of three-fourths of the normal gland in cats, dogs, rabbits and rats, fowls and pigeons. Halsted[1] and Hunnicutt[2] reported a series of partial thyroidectomies in dogs in which they failed to obtain the hypertrophy or hyperplasia of the remaining portion and, therefore, con-

*From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University, Cleveland, Ohio.

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cluded that Halsted's earlier and justly classic experiments[3] on the production of compensatory hyperplasia by partial removal were not due to thyroid removal, but to something else, possibly infection. Their failure to obtain compensatory hyperplasia in the second series was really due to the presence of available iodine either from the absorption of iodine painted on the skin or from contact with other dogs, or from inhalation of volatilized iodine from other dogs carrying iodine, or from other sources in the rooms.

4. If most of the thyroid gland is removed before or in the early stages of pregnancy and rigid steps are taken to exclude available iodine, the pups at birth will have enlarged thyroids, as first shown by Halsted,[3] while if available iodine is present, the pups will have normal thyroids.[4]

5. We have repeatedly found that a milligram of iodine given at weekly intervals is sufficient to prevent thyroid enlargement, although other pups of the same litter, living in the same kennel, and eating the same food, regularly developed goiter.

6. The thyroid gland has an extraordinary affinity for iodine, as can readily be shown by perfusion experiments *in vitro* or by injecting small amounts—5 to 20 mg. KI.—into the circulation.[5, 6] Experimentally then the proof is sufficiently complete to demonstrate the underlying principles of goiter prevention in animals and the ease with which they can be applied. From the practical standpoint, the first instance of preventing goiter on a large scale was accidental and in connection with the sheep raising industry of Michigan. Prior to the discovery of salt deposits around the Great Lakes, the future of the industry seemed hopeless, but with the development of the salt industry and its use by the sheep growers, goiter rapidly decreased. The salt contains appreciable quantities of both bromine and iodine and in places these elements are extracted on a commercial scale. The second instance of goiter prevention on a large scale was in brook trout. Some years ago the development of goiter in artificially raised members of the salmon family became alarming and many plants were abandoned on account of the disease. After considerable work, which led to the conclusion that the disease was simple goiter, we were able to completely prevent the disease in several hatcheries, by the use of very small amounts of tincture of iodine added to the water.[7] Later the attempt was made to substitute whole sea fish for part or all of the diet, which, likewise, proved to be, from the practical point of view, a cheaper and simpler method of complete prevention.[8] Similar preventive work with farm stock is being carried out under our direction in some of the valleys of British Columbia, where goiter was so prevalent that farmers were unable to raise hogs, cattle, horses, and chickens on account of myxedema (cretinism). Similar work in the prevention of goiter in hogs was recently reported by Smith.[9] He was able to completely prevent fetal myxedema by the use of potassium iodide to the mother during pregnancy. He, however, used quantities far in excess of those necessary to prevent goiter and myxedema. In spite of this knowledge of the ease and simplicity of goiter prevention in the lower animals, we know of no instance where the attempt has been made to systematically prevent or control the disease in children in large communities, especially those of the Great Lakes Basin, where goiter is so prevalent. Locally, we have been carrying out preventive treatment for the past six years at the Lakeside Hospital Medical Dispensary and have urged local

physicians to do so in their private practices. A great deal has been accomplished in this way, but as it is a public health matter the most practical and economic method would be to utilize the Public School System and the Board of Health. When the Medical Inspection of Schools is more or less independent of the Board of Health, it would be carried out through the Medical Director of Schools. This year it has been possible to begin such work on a large scale in the city of Akron, through the cooperation of the Superintendent of Schools, the Board of Education, and the County Medical Society.

It was decided for the present to limit the prophylactic work to the girl pupils, since adolescence is the most important goiter developing period and since at this period it occurs about six times more frequently in girls than in boys.

The plan now in operation was arranged from the standpoint of simplicity, practicability, economy, and the possible scientific value of the data obtained. Changes will doubtless be made as the work progresses. First a census of the condition of the thyroid gland was taken of all girls between the 5th and 12th grades inclusive and the findings recorded on individual cards, of which the following is a copy:

No.		Date
Name		School
Age	Weight	Physical Development
Grade		Class Standing
Tonsils-Adenoids		
Thyroid		1
Simple		2
Adenomas		3
Thyroid-tract		4
Duration		
Remarks		

The thyroid examinations of all pupils were made by a single examiner in order to make the standards used constant and the data obtained uniform. It is planned to take the census each year in the same way.

For the prophylactic treatment we have selected sodium iodide on the grounds of economy and ease of administration. Regarding the amounts that should be given, we have no data except those from animal experimentation. As has been pointed out repeatedly, exceedingly small amounts of iodine are needed. One milligram of iodine given weekly, by mouth, is ample to prevent goiter in dogs. In all our dispensary experiments with children we have used either syrup of hydriodic acid or syrup of ferrous iodide, in 1 c.c. doses, daily for two to three weeks, repeated twice yearly, and have recommended their use to clinicians solely because they were the only U. S. P. preparations sufficiently dilute to offset the tendency to use too large amounts.

We have, therefore, arbitrarily selected to use 2 gm. sodium iodide, given in 0.2 gm. doses each school day, for each pupil in the 5th, 6th, 7th, and 8th grades; and 4 gm. given in 0.4 gm. doses each school day for each pupil in the 9th, 10th, 11th, and 12th grades. These amounts will be given twice annually about the first of May and December, at the schools by the teachers or nurses. Bottles were distributed to the several schools, containing the solutions (0.2 gm. NaI in 5 c.c. H_2O and 0.4 gm. in 5 c.c. H_2O) in sufficient amounts to give each

pupil electing to take the prophylactic treatment a total of 50 c.c. A record was made both of those who took the treatment and of those who did not. All pupils will be examined annually and the thyroid conditions recorded. These amounts of sodium iodide provide approximately 1700 (1692) mg. of iodine for each pupil of the 5th, 6th, 7th, and 8th grades and approximately 3400 (3384) mg. for the 9th, 10th, 11th, and 12th grades. When one recalls that 25 to 30 mg. saturates the normal thyroid of 20 to 25 gm. and that the thyroid has an extraordinary affinity for iodine, it seems like a prodigious waste and we believe it is. The amounts used at the start were purposely made excessive to provide for any unknown factors and will probably be materially reduced.

Analysis of the Thyroid Examinations.—Three thousand eight hundred and seventy-two girls of the 5th, 6th, 7th, 8th, 9th, 10th, 11th and 12th grades were examined and the general result is given in the following tabulation.

TABLE I.

CONDITION OF THYROID GLAND.

	NORMAL	SLIGHT ENLARGEMENT	MODERATE ENLARGEMENT	MARKED ENLARGEMENT	ADENOMAS	THYROID-TRACT (PERSISTENT)
Total	1688	1931	246	7	39	594
Per cent	43.59	49.88	6.35	0.18	1.01	13.4

The thyroid glands were examined from the standpoint of *normals, slight, moderate,* and *marked enlargements, adenomas, persistent thyroglossal tracts* and the pupils for gross manifestations of *myxedema,* and *exophthalmic goiter.* No obvious case of either myxedema or exophthalmic goiter was found.

Under *normal* we have included all glands (a) which are not visible as a bulging of the skin across the trachea (b) having a barely detectable band of thyroid tissue across the trachea on palpation and (c) absence of well-defined thyroglossal stalk (so-called pyramidal process).

Those cases with enlarged thyroids have been divided into three arbitrary groups (1) *slight,* (2) *moderate* and (3) *marked* enlargement. Under *slight enlargement* we have grouped those cases with (a) visible bulging of the skin over the thyroid isthmus (except in the very stout children) and (b) a widened and thickened isthmial band or mass on palpation. If the isthmus can not be seen or felt, it can be felt by having the child swallow, while the finger or thumb is held against the trachea just below the cricoid cartilage.

Under *moderate enlargement* we have grouped those with gross deformity —bulging of the neck laterally from the enlarged lobes and marked bulging of the skin anteriorly from the enlarged isthmus. In approximately 93 per cent the right lobe was larger than the left, which is about the usual percentage.

Under *marked enlargement* we have grouped those cases with excessive deformity. One thousand six hundred and eighty-eight, or 43.59 per cent, of all pupils examined were classed as normal; 1931, or 49.88 per cent, were classed as slightly enlarged; 246, or 6.35 per cent, were classed as moderately enlarged (none of which had been operated upon); 7, or 0.18 per cent, were classed as markedly enlarged, of which two had been operated upon. This gives as totals 2184, or

56.41 per cent with enlarged thyroids and 1688, or 43.59 per cent, with normal thyroids. In 39 cases, or 1.01 per cent, adenomas, single or multiple, were detected. The smallest was approximately 2 cm. in diameter and the largest about 6 cm. These figures are of little value, since they include only the large superficial and favorably located ones.

The thyroglossal tract when present is very readily detected, either slightly to the right or left of, and rarely in, the midline. Only those which extended to the base of the thyroid cartilage were included. In many it was palpable to the hyoid bone. The very small pyramidal processes ending below the cricoid cartilage were not included. Five hundred ninety-four, or 13.4 per cent, of the cases had well-defined thyroid stalks. Physiologically the presence of thyroid tissue in the line of descent of the embryologic thyroid anlage indicates that the gland had undergone enlargement in intrauterine life, whereas normally the tract undergoes absorption beginning according to His[10] in the second month. The presence of large amounts of thyroid tissue about the foramen cecum—the so-called lingual thyroid—or of large masses between the hyoid bone and thyroid cartilage—so-called infrahyoid thyroids—are of the same significance. Excluding the rare congenital defects in the thyroid anlage, the amount of thyroid tissue in the line of descent of the thyroid gland may be used to determine the degree of normality of the thyroid gland in intrauterine life and as first pointed out by Streckeisen[11] it is an excellent index for determining the extent and degree to which a given district is affected with simple goiter. At Basel he found about 79 per cent of the cases coming to postmortem examination had persistent thyroglossal stalks. If the district is extremely goitrous and the mothers are not

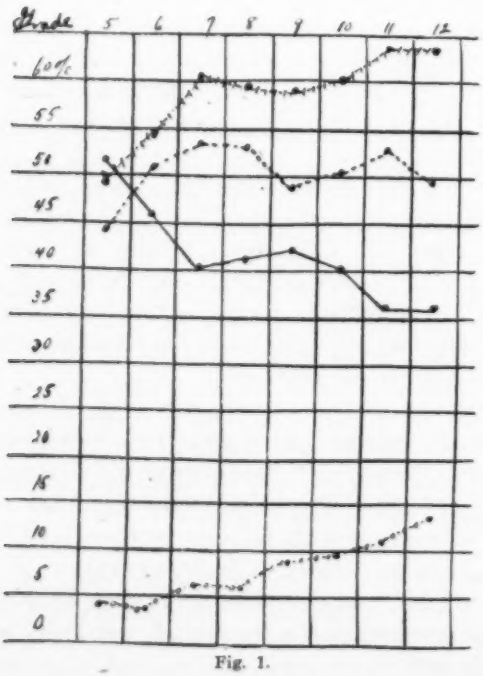

Fig. 1.

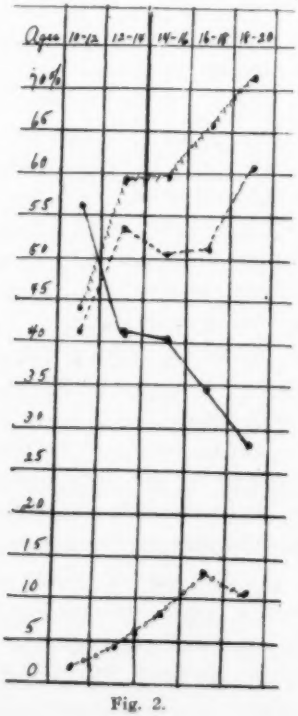

Fig. 2.

——— normals; - - - - - slight enlargements; -o-o-o-o- moderate enlargements; -/-/-/-/- total enlargements.

fed iodine during pregnancy, practically all children should have large persistent thyroglossal tracts. If the district is nongoitrous (e.g., sea coast regions) very few children will have persistent thyroglossal tracts.

Following the analysis further, the condition of the thyroid in relation to grades is shown in Table II and the accompanying curve chart (see Fig. 1); and in relation to age, in Table III and accompanying curve chart (see Fig. 2).

TABLE II.

CONDITION OF THYROID ARRANGED BY GRADES.

Grades	5		6		7		8		9		10		11		12	
	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
Normal	410	51.77	354	45.90	269	40.0	206	40.47	191	42.92	124	40.00	76	36.02	58	36.02
Slightly Enlarged	350	44.20	388	50.33	360	53.49	271	53.24	215	48.31	155	50.00	112	53.08	80	49.70
Moderately Enlarged	31	3.90	29	3.76	43	6.39	31	6.09	38	8.54	30	9.68	23	10.90	21	13.04
Markedly Enlarged	1	0.13			1	0.14	1	0.20	1	0.23	1	0.32			2	1.24
Totals	792	20.45*	771	19.91	673	17.38	509	13.15	445	11.5	310	8.0	211	5.45	161	4.16
Adenomas**	3	0.13	3	0.13	7	0.32	6	0.28	8	0.36	6	0.28	5	0.22	1	0.04

*Percentage of total pupils examined 3872.
**Adenoma percentage figured from the total enlarged thyroids 2184.

TABLE III.

CONDITION OF THYROID ARRANGED ACCORDING TO AGES.

Age	10-12		12-14		14-16		16-18		18-20	
	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
Normal	530	56.08	521	41.32	460	40.35	156	34.44	21	28.77
Slightly Enlarged	394	41.69	680	53.92	578	50.70	235	51.88	44	60.27
Moderately Enlarged	21	2.22	59	4.68	98	8.6	60	13.24	8	10.96
Markedly Enlarged			1	0.08	4	0.35	2	0.44		
Totals	945	24.41*	1261	32.56	1140	29.44	453	11.70	73	1.89
Adenomas	2	0.01**	11	0.52	18	0.84	8	0.39		

*Percentage of total pupils.
**Percentage of total enlarged thyroids.

The most rapid increase in the number of slight enlargements occurs between the 5th and 8th grades. This corresponds very closely with the rapid increase, between the 10th and 14th years. The average age of the 5th grade pupils was 10 years. Less than 2 per cent of the 5th grade were under 10 years and they were tabulated in the 10 to 12 age group.

The age group 18 to 20 contains less than 2 per cent of the total pupils, and while tabulated for the sake of completeness, the percentages are doubtless higher than the normal average for this age and properly belong to a special group with lower mental activity. The relation of thyroid enlargement to retarded mental development is an important subject, but our available data do not permit of further discussion at present.

DISCUSSION

The most valuable and accurate data of the incidence of goiter in America can be obtained from examinations of the public school population, because, in the first place it covers the most important ages when goiter develops; secondly, it gives the most complete census; and thirdly, no additional expense or additional effort is necessary. Up to the present time no organized and systematic effort has been made in this country to study the incidence of goiter in the school populations of large communities, even in the Great Lakes Basin—the largest and most densely populated of all goiter districts of North America.

The report by Hall[12] of the examination of 3339 students at the University of Washington is the most extensive available in American literature. Of the 2086 men with the average age of 20 years and 5 months, he found 374, or 17.93 per cent, with enlarged thyroids; 272, or 13.03 per cent, classed as perceptible; 92, or 4.43 per cent, classed as medium; and 10, or 0.48 per cent, classed as large. Of the 1253 women, with the average age of 19 years and 3 months, he found 388, or 30.98 per cent, with enlarged thyroids; 294, or 23.45 per cent, classified as perceptible; 85, or 6.79 per cent, classified as medium; and 9, or 0.7 per cent, classified as large. These figures demonstrate clearly the prevalence of goiter in the northwestern states. The group is too selective and the ages too advanced to give an average incidence percentage, because (a) the greatest incidence occurs during puberty, (b) a certain percentage of enlargements recede below the level of clinical detectability spontaneously and (c) a small percentage would have receded because of iodine feeding.

In the Great Lakes Basin, Olsen[13] reports the examination of 606 women and 193 men, presumably between the ages of 18 and 60, at Chicago. Among the women, he found an average of 17.87 per cent affected and among the men 6.72 per cent. The figures emphasize the frequency of thyroid enlargements, though they are very much lower than would be obtained from a similar number of examinations during the school age, on account of the factors of spontaneous or induced regression of the thyroid enlargements and of migrations from nongoitrous districts, which his figures necessarily include.

In Europe the statistics of Schittenhelm and Weichardt[14] deal with the incidence of goiter in the school populations of certain districts of Bavaria, where goiter is prevalent. Using very liberal standards, they report incidences as high as 77 and 89 per cent of the school population affected.

In the Vosges mountains of eastern France and Alsace, MacAuliffe[15] has recently reported the examination of 2311 children between the ages of 2 and 15 years. He found 288, or 12.5 per cent, affected. A comparison of our data with the data cited above is not possible. We use a much more rigid standard of normal, both clinically and anatomically. Anatomically, the strictly normal gland does not exceed 0.5 gm. thyroid per kilo of body weight, though many European writers, especially those in the Alpine goiter districts, allow as much as 1.0 gm. per kilo. In dogs, the normal thyroid gland does not exceed 0.3 gm. per kilo. Clinically, in the normal gland the isthmus can barely be felt, but the lateral lobes can not be felt.

The question of the production of exophthalmic goiter by the use of iodine may be mentioned briefly. Some Swiss writers, like Oswald[16] take the extreme

view that iodine should never be used in goiter, because of the danger of producing exophthalmic goiter. Pineles[17] and Kocher[18] take the more moderate ground that iodine should be given cautiously to neurotic individuals with goiter. Our experience has led us to the conclusion that the risk of inducing manifestations of exophthalmic goiter from the use of iodine in physiologic doses is exceedingly small, even in those cases with large hyperplastic thyroids; i. e., the kind of thyroid enlargement which would permit of the most rapid formation and excretion of the iodine-containing hormone. The extent to which iodides are used in general medicine and surgery and the rarity of the development of signs of exophthalmic goiter is the best index of the danger. Iodine is usually employed in immensely large doses; 0.2 to 0.4 gm. NaI daily for 2 weeks would offer a great excess over the amounts necessary to saturate even the largest thyroids and probably much smaller amounts would suffice in man, as it has been proved to do in the lower animals.

While the danger of causing symptoms of exophthalmic goiter probably varies with the size and degree of active hyperplasia, all authors agree that the important factor in determining such symptoms lies outside the thyroid, either in the nervous system, or some gland like the adrenal, and antedates any thyroid changes. Klose[19] has reported the production of exophthalmic goiter in nervous fox terrier dogs, by the injection of sodium or potassium iodide in 0.6 gm. doses per kilo. Those experiments were soon discredited by the work of Bordenhewer[20]. No one else has suggested any danger from the use of iodides in the case of nongoitrous individuals, except the well-known acute iodism, which affects a small percentage of people, and, so far as known, is not related to thyroid activity. Cases with definite manifestations of exophthalmic goiter should not be given iodine, although there are cases (or better, stages) of the disease which are distinctly benefited by iodides.

The use of desiccated thyroid has well-known dangers after adolescence—mainly because of the large doses used. Both economically and practically, it would not be suitable for general use, as a prophylactic agent.

SUMMARY

In a complete census of the condition of the thyroid gland in the girls from the 5th to 12th grades of the school population of a large community in the Great Lakes goiter district, it was found that 1688, or 43.59 per cent had normal thyroids; 2184, or 56.41 per cent, had enlarged thyroids; and 594, or 13.4 per cent, had well-defined, persistent thyroglossal stalks. The community lies near the southern edge of the goiter district and it is suggested that communities near the lakes would show a higher incidence. The method of prophylaxis proposed is in operation.

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TRANSPLANTATION OF THE THYMUS IN RABBITS—RELATION OF THE THYMUS TO SEXUAL MATURITY

By David Marine, M.D., and O. T. Manley, M.D., Cleveland, Ohio.

THE objects of these experiments were to obtain more definite data on the transplantability of the thymus; and if transplantable in accessible locations, to utilize this means of studying its behavior in relation to sexual maturity and breeding.

The thymus normally undergoes a striking atrophy or involution at puberty. It seems well established by the work of Paton and Goodall, Henderson, Calzolari and others, that removal of the gonads before puberty delays thymus involution; that thymus removal hastens sexual maturity in rabbits; and that animals allowed to breed show earlier thymus involution than those not so used.

In our experiments, we have removed all the main thymus mass (exposing the gland by splitting the sternum to the third rib) except the upper portion of one of the cervical cornua, and have transplanted small (2 to 3 mm.) fragments into the subcutaneous tissue of the abdomen. Contrary to the results of Renton

that transplants in the subcutaneous tissues did not survive, we have found that it can be readily transplanted in this location in sexually immature rabbits. Whether the peritoneal or subperitoneal tissues are still more favorable, as some authors state, we have no data.

As with the spleen, only autotransplants have survived. Immediately after thymectomy, as above described, two autotransplants were placed in the subcutaneous tissue of the abdomen of each of 8 rabbits. Each rabbit was between three and one-half and four months old. Six of these rabbits have been observed for three months, and the transplants examined directly at monthly intervals. Two females were kept with one of the males. Examination at the end of the first month showed that both were pregnant, which is earlier than rabbits usually breed. At the gross examination, the transplants in all three seemed negative, though the enlarging breasts made the examinations unsatisfactory. One transplant area was removed from each and examined histologically. In one female, there was an active transplant, while in the other female and the male the transplants had undergone nearly complete absorption. Of the remaining five, two died before the end of the first month. The remaining three, (two females and one male) had active transplants, the male and one female having large 4 mm. transplants, showing clearly that growth had occurred.

At the beginning of the second month, the female with the large thymus transplants was bred, and at the end of the second month these transplants could not be found, though on account of the lactating breasts the examination was not satisfactory. The male with large transplants at the end of the first month had active transplants, possibly larger than at the first examination. The unbred female also had active transplants.

Again at the examination after three months, the male and female (now over seven months old) kept isolated, still had active transplants. One from each was removed for histologic examination. Microscopically, these are encapsulated vascular masses of compact lymphoid tissue. There is no increase in fibrous tissue about thymus transplants as is usually seen around spleen grafts.

The remaining four (used for breeding) were also examined at the end of three months, and the five remaining transplant areas removed. Definite but small masses of thymus lymphoid cells were found in two.

These experiments, which are preliminary, show that in sexually immature rabbits, fragments of thymus autotransplanted into the subcutaneous tissue of the abdomen after thymectomy may "take," grow, and survive. There is clear though scant evidence in confirmation of other observers' results, that thymus removal hastens sexual maturity. Also, as others have found, utilization of rabbits for breeding hastens involution of the thymus. Our experiments show that this applies to the transplanted thymus as well, and this suggests that a specific nerve influence is not essential for these involutionary changes.

ON THE COMPLEMENT-FIXATION TEST IN TUBERCULOSIS WITH BESREDKA'S ANTIGEN*

By J. Bronfenbrenner, Ph.D., Boston, Mass.

REFERRING to the value of auscultation as an aid in early diagnosis of the tuberculosis, Laennec wrote in the preface to his capital work, "I may say that no one who has made himself expert with this method will have occasion to say with Baglivi, 'Oh, how difficult it is to diagnose the disease of the lungs.'"

In spite of the great contribution rendered by Laennec himself, in spite even of the epoch-making discovery of Koch, the early diagnosis of tuberculosis is still a problem to be solved, even as it was one hundred years ago in the days of Laennec.

The difficulties confronting the students of tuberculosis are many: but essentially the problem is difficult because of the extreme pleomorphism of clinical manifestations of tuberculosis and because of peculiar lack of uniformity in the course of this disease in different individuals affected, depending on their susceptibility or individual resistance, which are often subject to temporary fluctuations.

Although methods for the early diagnosis of tuberculosis are still wanted, the wide distribution of this disease is fairly well established. In fact, tuberculosis, not unlike syphilis, must be constantly kept in mind in making a diagnosis, whatever may be the clinical picture of the case.

Unfortunately, the manifestations of syphilis, are no less pleomorphic than those of tuberculosis, and in many instances they may amazingly simulate the clinical picture met with in tuberculosis. In cases where material for bacteriologic diagnosis of tuberculosis is not at hand, Wassermann reaction is practically the only method for the differential diagnosis. However, as the Wassermann test itself is not absolutely specific, and as, on the other hand, it is not always present even in the cases with definite signs of lues, this test does not offer an absolute means of differentiation between the two conditions.

In the quest for a reliable method for a diagnosis of tuberculosis, numerous investigators repeatedly attempted to apply the new methods used in diagnosis of other infectious diseases, but their attempts were crowned with partial success only. The use of agglutination precipitation, miostagmin or epiphanin reactions was found to be of little diagnostic value.

The remarkable usefulness of Wassermann reaction especially stimulated the efforts of numerous investigators along the lines of application of Bordet and Gengou reaction to the diagnosis of tuberculosis. The earlier efforts along this line were not very encouraging. This could be due to several causes. It is possible that (due to the walled-off nature of the lesions and the slow process of the disease in certain cases) there may be none or a very small amount of immune bodies present in the circulation. Moreover, the concentration of circulat-

*From the Department of Preventive Medicine, Harvard University Medical School.
Read before Laennec Society of the Johns Hopkins Hospital, Feb. 26, 1917.

ing antibodies is subject to constant and quite marked daily fluctuation in the same patient. Besides, the antibodies in tuberculosis may not be to any great extent of the nature of amboceptor. Again tuberculous amboceptor, as suggested by Davidowitch, may be more thermolabile than most others, and since complement deviation is usually performed with inactivated serum, the amboceptor may be largely[1] destroyed in heating; thus the amount remaining in the serum may not be large enough to be detected even by the delicate method of complement fixation.

In addition to the difficulties due to the apparent peculiarity of the immune processes in tuberculous individuals and resulting variations in concentration of specific amboceptors the lack of proper antigens seems to have been greatly responsible for the irregularity in the results obtained by the different authors in their study of the complement fixation in tuberculosis. The study of the literature on this subject reveals the fact that suspensions of living or dead bacteria were found most reliable of all the different antigens used, but even with such antigens the results obtained were not entirely satisfactory. In 1913, Besredka succeeded in cultivating tubercle bacilli on an entirely new medium. The fact that on this medium the organism showed some hitherto unknown properties induced him to try the antigenic properties of his new cultures for the complement-deviation test. Successful results obtained by Besredka and Manoukhine in their preliminary experiments were fully confirmed in several laboratories. It was found that the complement deviation with Besredka's tuberculin gives a very high (90 to 95 per cent) percentage of positive results in cases of clinical tuberculosis and at the same time the occurrence of the reaction in cases in which tuberculosis could not be detected clinically, was limited to less than 10 per cent.

The antigen of Besredka consists of autoclaved filtered culture of tubercle bacillus grown on a new liquid medium, composed of alkaline broth to which is added egg white and egg yolk.[2]

As this medium can not be made in large quantities on account of its rapid deterioration and has to be made fresh every time, the composition of the antigen made from it may vary in different batches. First of all, the chemical composition of individual eggs, and consequent variations in the amount of alkali necessary for suitable clarification, vary to a marked degree. Besides directly affecting the chemical composition of the antigen, these fluctuations in the medium may also at times enhance or inhibit the growth of bacteria and thus still further influence the respective values of different batches of tuberculin for complement fixation.[3]

Another important source of variation was found in the apparent strain specificity displayed by different tuberculous sera. It is easy to demonstrate

[1]It is known that about 50 per cent of hemolytic amboceptor is destroyed by inactivation.

[2]This medium is made in the following way: Each, white and yolk of an egg are diluted with ten volumes of water and filtered through a hard paper (Chardin). The yolk solution is carefully clarified by the gradual addition of sodium hydroxide. Both solutions are autoclaved and kept separate. Just before using, one mixes 10 volumes of the sterile alkaline veal infusion (prepared without peptone, salt, or glycerin) with two volumes of the sterile egg white solution and one volume of the sterile clarified egg yolk solution. This mixture is placed in sterile tubes and is used without further sterilization. As this medium deteriorates on standing, it should be made fresh each time. Our experience fully confirmed the statement of Besredka about the rapid growth of certain strains of tubercle bacillus on this medium. It is true, not all the strains seem to grow with equal facility, but certain strains, like H-46, H-48 from Dr. Baldwin, H-12, H-29, H-31, from Dr. Theobold Smith, R-3 from Dr. Paul Lewis, and H-389 from Dr. W. H. Park showed very definite growth within the first few days after planting.

that certain tuberculous sera may fix the complement in the presence of certain selected samples of Besredka and other antigens. It is thus, that among 50 cases of diagnosed tuberculosis only in 18 we found fixation with every one of the three samples of Besredka's tuberculin. In 26 cases we obtained fixation with two samples out of three and in two cases the fixation was obtained with one sample of tuberculin only.[4] That the selective fixation with different antigens is due to the strain specificity and not to some technical error is evidenced by the fact that in many instances in which sera were examined repeatedly the results of such examinations invariably confirmed the selective tendency on the part of the sera.[5]

The greatest and most important source of variations in the antigenic value of different batches of Besredka's tuberculin lies, however, in another direction. Already in the beginning of the study it appeared that a number of sera giving a positive Wassermann reaction often showed fixation with Besredka's tuberculin also. As not in all of these cases one could find clinical evidence of tuberculosis, the first explanation for this coincidence of the reactions, naturally was that the sera of syphilitics, having high lipotropic coefficient, fixed the complement also with the tuberculin of Besredka on account of lipoids contained in it. The study of a number of sera giving a positive Wassermann reaction with this point in mind showed, however, that the complement-deviation test with Besredka's antigen is not lipotropic in nature. Whenever present in serums possessing high lipotropic property, it depends on the presence of a separate antibody having its own index different from the lipotropic index in the same serum. Moreover, when the serum deviates the complement in presence of both Besredka's tuberculin and pure lipin antigen, each of the two antibodies can be exhausted from such serum independently of each other. On the other hand, Besredka's tuberculin can be freed of its lipins without losing its property to fix complement in presence of tuberculous sera. The lipins may be extracted by fat solvents, but the easiest method was found to be that of separation of the protein fraction by precipitation.[6]

The presence in the same serum of the property to fix complement with both antigens independently can be reproduced in experimental animals. When present in human beings (as well as in animals), the lipotropic antibody disappears under salvarsan treatment, whereas the tuberculous antibody persists.

The high percentage of negative reactions among clinically nontuberculous (92 per cent), together with the other proofs of the high degree of specificity

[3]This consideration should be given a great deal of attention, as some of the batches of antigen sent to us by Besredka were more anticomplementary than others without being more antigenic; hence it is necessary to vary the amounts of tuberculin used for the test with each batch of antigen.

[4]Among 4000 sera examined in collaboration with J. Rockman and M. J. Schlesinger, with a view of establishing the nature of these variations in the respective fixing power of different samples of Besredka's antigen, the reaction was found positive with one or more samples of this tuberculin in 232 instances. Each of the 232 serums thus selected was reexamined with seven different preparations of tuberculin. We found that in 167 cases (or 72%) out of 232 the fixation was obtained with at least four antigens out of seven used. Out of the remaining 65 cases, in 23 at least two tuberculins fixed the complement, and in 12 cases the crude tuberculin of the New York Board of Health was the only one confirming the results obtained with the tuberculin of Besredka. In 30 cases out of this total of 232, the fixation occurred only with the tuberculins of Besredka.

[5]The existence of strain specificity in tuberculosis may be one of the contributing factors in causing much variation in the results obtained by different investigators in the complement-deviation test for diagnosis of tuberculosis.

[6]Such precipitation of the antigenic fraction of tuberculin also offers the possibility of using a standard number of units of antigen and thus eliminating variatons due to the quantitative differences in specific properties of different samples of tuberculin, without increasing the chance of obtaining lipotropic reactions.

of this reaction, seem to indicate that the comparatively frequent simultaneous occurrence of the complement-deviation test with Besredka's antigen and the Wassermann reaction in syphilitics is not due to some technical error.[7] In fact the study of a number of cases from this point of view brings out some very interesting statistics. Thus Jones,[8] subjecting to the Wassermann test 251 unselected cases coming to the public tuberculosis clinic, found that 73 among them had a positive Wassermann. In the series of 346 tuberculous inmates of the Boucicaut Hospital, 19 per cent gave a positive Wassermann test, according to Letulle[9] and of those only 10 individuals (out of 64 reacting) were aware of their syphilitic taint or had definite signs of it. Our own results, as well as these and other similar observations of different authors, which came to our attention since our earlier work was published, suggest that occurrence of the complement fixation with Besredka's antigen in the cases in which Wassermann reaction is also present may be due to the fact that either syphilis, as such, or the antisyphilitic treatment markedly lowers the resistance of the patients so as to make them either more susceptible to new infection with tuberculosis or to render them less resistant against the progress of this disease previously contracted.

Some authors, it is true, did not find any high frequency of occurrence of tuberculosis among syphilitics (as interpreted by the complement-fixation test). However, if one takes into consideration the class of patients upon which the test is performed, this discrepancy can be easily explained. In our series of syphilitics, we dealt with patients of all ages, greatly exposed to infection with tuberculosis in their factory surroundings, and even more so in the unhealthy conditions of their life in the slums. The material of Craig, who found less than 1 per cent of tuberculosis in luetics, for instance, consisted, on the contrary, of a group of young men of military age comparatively free from tuberculosis at the time of their admission to military service and who ever since their admission were placed in exceptionally good hygienic conditions.[10] It seems, therefore, that for a nonselected group of patients (as represented, for instance, by the admissions to the general hospital or dispensary) the simultaneous occurrence of fixation with tuberculin and lipoid is quite frequent and is due to the simultaneous coexistence of two diseases. Such a conclusion is apparently borne out by clinical observations of such men as Fournier, C. F. Marshall, Douty, F. H. Andrews, Sir Jonathan Hutchinson and others.[11]

As for the percentage of the occurrence of the reaction in different stages of tuberculosis when a purified antigen of Besredka is used, we wish to present these approximate figures: First stage, 84 per cent; second stage, 94 per cent; third stage, 15.3 per cent; clinically nontuberculous (controls), nonsyphilitics, 5 per cent.

The question of surprisingly low percentage of positive results in far advanced cases was especially investigated. In addition to the Besredka antigen we examined a large group of such cases (from Leech Farm, Pittsburgh), with the antigens of Craig, Corper and Calmette, and more recently also with antigen

[7] In this connection see results of Fraser, who, using various antigens not containing lipoids came to the conclusion that sera of syphilitics often deviate complement in presence of tuberculosis antigens (bacillary emulsions). Ztschr. f. Immuntitäforschung., Orig. 1913, xx, 291.

[8] Jones: Med. Record, Sept. 2, 1916.

[9] Letulle: Bull. de l'Acad. de méd., Paris, lxxviii, No. 16, 589.

of Miller. Although it was possible to observe a slight variation in the results obtained with respective antigens, in general they reacted no better than that of Besredka.

As for the reason for this failure of advanced cases to give fixation, there can be at least two offered tentatively: one is that the resistance of the patient has been exhausted, there is no new antibody formation; and the other, that the circulating antibody is taken up as formed by the combination with antigen which may greatly increase during the last stages of the disease.

While the results of experiments on animals in the case of tuberculosis have but a relative value, it might be stated that the general tendency of these results, however, also suggest that the concentration of circulating antibody depends on the degree of resistance of the individual animal. Thus, rabbits seem to develop antibody and show the fixation of complement if infected with the human strains of tubercle bacillus, but usually fail to fix the complement when infected with bovine. In guinea pigs the results are even more convincing. The animals give complement-fixation as early as the fourth or fifth day after infection, but uniformly fail to fix complement during the fourth to sixth week of the disease.

Before closing I would like to give in brief the procedure followed in performing the test.[11]

Fresh serum is used, thus obviating the danger of destruction of antibodies due to heating. The human serum is titrated for the amount of complement present. Such titration is performed with washed human red blood cells which have been previously sensitized with one unit of amboceptor. (The antihuman hemolytic system is used to avoid the uncontrollable factor due to the presence in human serum of varying amounts of natural antisheep amboceptor.) At the same time guinea pig serum is titrated for its complement content, using human erythrocytes sensitized with the same amount of amboceptor. In setting up the test, one adds a sufficient amount of guinea pig serum to bring up the amount of complement already present in the human serum to two units. The antigen is then added and the tubes are incubated. At the end of the incubation, erythrocytes sensitized with one unit of amboceptor are added and after another period of incubation the progress of hemolysis is noted. We found this method to be very sensitive, its delicacy being entirely due to the minute amount of complement available for fixation and the absolute control of hemolytic system. Another advantage is in the fact that by using active serum we do not miss weak cases, where heating would have destroyed the antibody. As for the antigen to be used in the test, although we found Besredka's antigen to give the best results, we must admit, that the preparation of antigen as suggested by Miller and Zinsser is much simpler, and if the results obtained with it are as good as those obtained with Besredka's tuberculin, it seems that such antigen might be more practical for the use in the test.

It is evident that a successful application of the complement-fixation re-

[10]As a characteristic example of another extremity showing the importance of ascertaining the social status of the patients on whom such tests are performed with the view of drawing conclusions as to frequency and interdependence of these two diseases I wish to quote from Dr. N. B. Potter's article the results of Dr. Tedenshi who found in his ten years' service as a physician in a prison that 70 per cent of the cases of pulmonary tuberculosis had developed upon a luetic soil. Tedeschi: Studium, Napoli, 1910, iii, 343, 377.—Potter: Am. Jour. Med. Sc., Dec., 1916, vclii, 6, p. 823.

[11]Oxford System of Syphilis, 1914, iii, 197.

[11]A detailed discussion of the technic is given in American Journal of Syphilis, 1917, i, 2, p. 406.

action for the diagnosis of early tuberculosis is already at hand. There is very little doubt that fixation indicates active tuberculosis, especially if the reaction remains positive when repeated at intervals. In arrested or cured cases the reaction eventually becomes negative. The value of the negative outcome of the test is only relative (as it is also in case of the Wassermann reaction), however, inasmuch as in advanced cases it is negative as well. In such cases the absence of circulating antibody may indicate the failing of resistance.

A CASE OF CONGENITAL CYSTIC KIDNEY IN WHICH A TUBERCULOUS PROCESS WAS SUPERIMPOSED*

By Paul G. Woolley, M.D., Cincinnati, Ohio.

H. G., Hospital No. B-876, a married negress, 41 years old, was admitted to the Cincinnati General Hospital on February 5, 1917, complaining of shooting pains in the region of the right kidney.

Family History.—Negative.

Past History.—She had had measles and whooping cough. At the age of 18, she had typhoid. In November, 1915, she was operated upon for a renal tumor. Menstruation commenced at the age of 13½, and has been somewhat irregular and the flow slight. She has been married for 13 years. Her husband is living and well and they have three children. There have been no miscarriages.

About a year before the operation of November, 1915, she had the same sort of pain of which she complains now; i.e., shooting pain radiating down to the bladder and around to the back. She was unable to do much work because of lassitude. She had some little pain after urinating and at times she passed blood. The operation disclosed a right kidney studded with cysts which varied in size from a pinhead to a walnut and also some perirenal tissue cysts. The whole organ was about twice the normal size. The cysts were all punctured.

An x-ray report stated that "a second examination of the right side failed to show the outline of the right kidney. No tumor mass was seen. Colon plates show the hepatic flexure and transverse colon pushed downward by a tumor mass."

[In March, 1915, the patient had been in the hospital and at that time a functional test (phenolsulphonphthalein) showed a normal output of dye, but decreased fluid on the right. At that time operation was refused.]

About three weeks after the operation, while the patient was stooping over a pan washing her face, something seemed to break inside of her, and from this time she has had pain and has been worried. She said that during the past summer she was "puffed up all over her stomach," and could not eat. The week before the last admission she had pain on urination and some bleeding which made her feel better. She has had to urinate two or three times during the night since this time, whereas previously she used to get up every 15 minutes. Now she has chills, irregularly, several times a week (five to six times). With these chills, which are nocturnal, she has no renal pain or sweating.

Present State.—The patient is a thin, elderly woman lying quietly in bed. Her eyes react to light and accommodation. The nose, eyes, ears and neck are negative. The tongue appears normal. The chest shows symmetrical expansion and resonance. Over the right lung there are no râles heard, and no evidence of consolidation, but there is a friction rub over the middle lobe. The cardiac rhythm is normal, and the pulses equal and even. There is abdominal tenderness over both kidneys. The right kidney seems to be enlarged and cystic.

Cystoscopic examination shows that the mucous membrane of the bladder is fuzzy

*From the Mary M. Emery Department of Pathology of the University of Cincinnati. and the Pathologic Institute of the Cincinnati General Hospital.

in appearance, with alternating reddish and whitish areas. There is one dark hemorrhagic area above the ridge. The ureters are hard to catheterize; the right gives a rapid flow of clear urine; the left a small amount. Functional test with carmine red gave no results through the left kidney in 30 minutes.

February 7.—There is a large mass in the right renal region which is not related to the liver dullness, and which feels cystic. It is about twice the size of a normal kidney. A catheterized specimen of urine showed albumin for both sides, many leucocytes, a moderate number of red cells, and a few casts.

February 12.—The patient complains of frequent and burning urination.

February 14.—She is weaker and has pain in the left side.

February 18.—Died.

CLINICAL DIAGNOSIS.—Double cystic kidneys.

AUTOPSY PROTOCOL.

The body was that of a slender, emaciated, coffee-colored negress, with not very kinky hair. Rigor mortis was present; postmortem lividity was faint. There was a slight edema of the ankles. The peripheral lymph glands were not appreciably enlarged. The pupils were equal. The conjunctivæ were pale. The upper teeth were replaced by an artificial plate. All except the anterior lower teeth were missing and those that remained were in good condition. In the right flank posteriorly was an old atrophic incision 14 cm. long, that reached from the lower border of the last rib to the crest of the ilium 8 cm. posterior to the anterior superior spine. The breasts were atrophic and flaccid and contained no nodules. There were lineæ albicantes on the abdomen above the pubis and on the upper anterior surface of the thighs. The lower margin of the liver lay 8½ cm. below the ensiform and 3½ cm. beneath the costal margin in the right mammillary line. The omentum was coiled into a solid strand chiefly above the transverse colon and was punctated with innumerable fine hyaline and gray nodules that resembled miliary tubercles. It was adherent to the abdominal wall above the left inguinal ring. The peritoneum everywhere over the surface of the intestines and over the parietes was studded with fine translucent nodules resembling miliary tubercles, many of which were pigmented, the pigment forming, as a rule, a ring about the tubercles. The appendix was *in situ* and, except for the presence of the tubercles upon its surface, seemed to be healthy. In the pelvis the tubercles were larger, less discrete, and far more numerous than elsewhere in the abdominal cavity. There was no increased peritoneal fluid. When the sternum was removed, the lungs did not collapse, largely because both pleural cavities were completely obliterated with old adhesions. The right kidney was adherent by old adhesions to the hepatic flexure of the colon and the left kidney was adherent by old adhesions to the splenic flexure. There were old adhesions between the dome of the liver and the diaphragm and in these adhesions were very numerous tubercles. The mesenteric and retroperitoneal lymph glands were all hyperplastic, distinctly pale and moist, and in many of them there were areas that appeared to be due to caseation.

The right kidney (1,010 grams), was firm and seemed to be composed almost entirely of a large number of cysts varying in size from a few millimeters in diameter to several centimeters. The capsule was apparently completely adherent and on section it appeared that some of the cysts were filled with a rather clear, almost serous fluid; others contained an inspissated, dark colored material containing blood; and still others contained a material rather thick like pus. There were other areas which were not cystic which were filled with a yellowish caseous material and these areas were typically tuberculous. The left kidney had the same gross appearance but on section showed no evidence of tuberculous process but had all the appearances of a typical cystic kidney. The liver was of fair size but very flabby. The surface was scarred almost generally with the tags of old adhesions. Scattered here and there throughout the substance in both lobes were very numerous subcapsular cysts, all, so far as could be seen, filled with clear fluid. One of these cysts, the largest, measured 5½ cm. in diameter. There were occasional areas that resembled small caseous spaces. There were occasional areas that resembled small caseous tubercles. One of these seemed to have originated in the neighborhood of a bile vessel for it had a central greenish nucleus. The gall bladder was filled with a mucoid brownish bile and the ducts were patent.

The lungs, after removal from the body, were almost completely collapsed. The

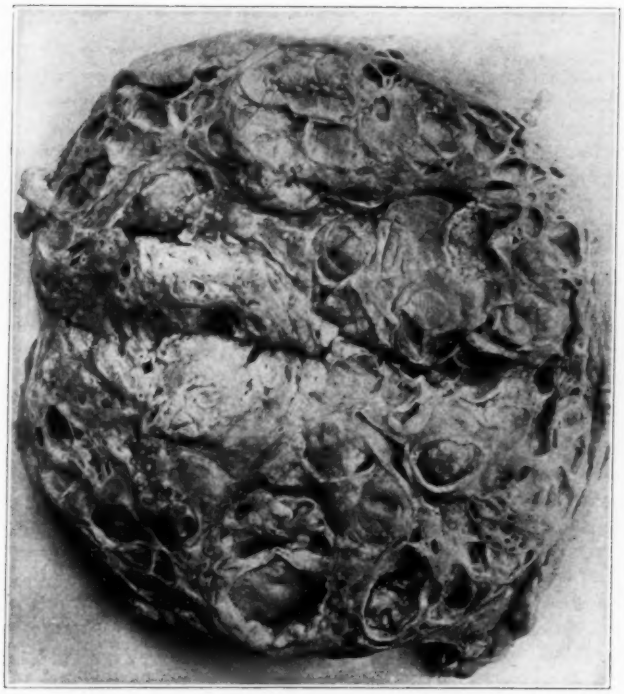

Fig. 1.—Photograph of the right kidney showing the cysts, some of them filled with caseous material or tubercles, others patent. Many small, almost miliary tubercles are also visible.

Fig. 2.—Photograph of a section of the liver to show the thin-walled, somewhat trabeculated cystic spaces.

pleura was generally thickened and beneath it and in the substance of both upper lobes, there were numerous firm, fibroid nodules which on section seemed to be obsolescent pigmented calcareous tubercles. There were a few such nodules in the lower lobes. The lower lobes were bound together by old adhesions. The heart was small and flabby. The pericardium was smooth. The coronaries were slightly tortuous but not evidently sclerotic. There was nothing unusual in connection with the tricuspid or pulmonary orifices. The foramen ovale was open but protected by a competent valve. The mitral and aortic valves were healthy. The aorta was smooth throughout and showed nothing more than scattered patches of subintimal fatty degeneration. The myocardium was pale and friable. There was no evidence of fibrosis. The spleen was of normal size. The surface was tagged with old adhesions and the color was pale. On section, the pulp was distinctly pale and the consistency was normal. The Malpighian bodies were not visible and at one or two points there were small gray areas which resembled tubercles. Both fallopian tubes were convoluted and the convolutions were bound together by old adhesions. Also both tubes were large, the enlargement being apparently due to increased semisolid contents. Except that the ovaries were more or less surrounded by old adhesions there was nothing abnormal about them. The uterus was of normal size.

The urinary bladder contained a small amount of cloudy blood-tinged purulent urine. The whole mucous membrane had an irregularly congested and generally moist appearance. The left ureter was evidently healthy. The right ureter, in its lower 7 cm., was the seat of a well marked, chronic, ulcerative tuberculous process. The right fallopian tube appeared to be a practically solid mass of caseous material. The left tube was partly caseous, partly suppurative. Around the cervical opening of the uterus there was a slight amount of erosion but nothing else. The vagina and body of the uterus seemed to be healthy except for the presence of a few small fibromas in the myometrium. The mucous membrane and submucosa of the rectum were edematous but showed nothing else unusual. In the large intestine there was nothing unusual except a moderate edema of the muscular coat. In the small intestine there were numerous ulcers. In the cecum there was one very large transverse, evidently tuberculous, ulcer which measured 7x3 cm., the base of which was congested and in places covered with a rather adherent, greenish colored pseudomembrane. Above the cecum in the first 10 cm. of the ileum, were very numerous small ulcers with thickened edges in which one could see occasional tubercles. Above this there were other scattered ulcers most of them small but all of them more acute than the cecal ulcer.

ANATOMIC DIAGNOSIS.—Congenital cystic kidneys and liver; chronic tuberculous nephritis; chronic tuberculous salpingitis; chronic and acute tuberculous enterocolitis; chronic tuberculous cystitis and (right) ureteritis; miliary tuberculous peritonitis; chronic miliary tuberculous lymphadenitis; obsolescent pulmonary tuberculosis; miliary tuberculous hepatitis and splenitis.

REMARKS.

It is interesting to speculate upon the course of the tuberculous process in this case, and to wonder whether it originated in the lungs or in the urogenital tract. The evidence furnished by the distribution of the peritoneal lesion tends to make it clear that the intestinal tract was not primarily involved for the peritoneal tubercles did not show the peculiarity of distribution which goes with intestinal ulcers; there was no grouping of the tubercles below the ulcers in the peritoneum. It seems most plausible to imagine that the process began with a pulmonary lesion which healed after bacilli had been distributed to the kidney and the fallopian tubes, in which places the process progressed.

The case illustrates exceedingly well how little kidney substance is required to preserve the health of the body. In these two enormous organs there was scarcely a macroscopic bit of kidney parenchyma, and yet up to the time the patient was overwhelmed by the tuberculous process, she lived in apparent comfort and health.

LABORATORY METHODS

THE EFFECT OF THE NATURAL ANTISHEEP HEMOLYSIN CONTENT OF HUMAN SERUM ON COMPLEMENT-FIXATION TESTS*

By Anna I. van Saun, Albany, N. Y.

ONE of the principal objections to the antisheep hemolytic system most commonly used by serologists for complement-fixation tests is the fact that nearly all specimens of human sera contain natural antisheep hemolysin. This natural antisheep hemolysin is sometimes present in the patient's serum in such large amounts that the addition of artificial antisheep hemolysin is unnecessary for the production of hemolysis in the serum control tubes and many workers have found that in some cases this natural hemolysin will obscure evidence of specific fixation in complement-fixation tests.†

A number of modifications of the original Wassermann test have been devised to overcome this difficulty as, for example, that of Noguchi,[2] which uses an antihuman system, that of Hecht-Weinberg[3] which makes use of both the complement and antisheep hemolysin present in the patient's serum, and that of Bauer[4] which also depends on the presence of natural antisheep hemolysin in the patient's serum.

Kaliski,[5] in 1910, instituted a modification of the Bauer test which he describes as follows: "The tubes containing the serum to be tested, complement and antigen extract are incubated, emulsion of sheep's corpuscles added and incubated again. To the tubes showing no hemolysis or only partial hemolysis, two units of artificial amboceptor are added and the tubes placed in the incubator again. After the second incubation the presence of antisheep amboceptor is indicated by the degree of hemolysis."

The absorption method of Rossi[6] has been very generally used as a means of getting rid of natural hemolysin in serum. Olmstead,[7] in 1914, found through a series of comparative tests on fifty-two sera treated by this method, and tested by the method used by McNeil[8] in the Research Laboratory, Department of Health, New York City, that the natural amboceptor content of human serum makes but little difference in the Wassermann test if the readings are made as soon as serum and antigen controls are completely hemolyzed.

In the course of two years' experience in the State Laboratory with over

*From the Division of Laboratories and Research, New York State Department of Health, Albany, N. Y.

†In a recent article on the Wassermann test Ottenberg[1] states that this natural antisheep hemolysin content of human sera is far more often demonstrated when a fixed amount (so-called excess) of complement (one-tenth c.c.) is used for the test and the balance of the system determined by means of an amboceptor titration as Wassermann and his followers advocate. Ottenberg seems to find that complement is more often overactive than underactive, and advocates a standardization of the system by means of a complement titration. In my experience I have found just the opposite to be the case. I have very seldom observed a mixture of complement that would titrate higher than a 1 in 10 dilution. Usually the titer would run about 1 in 8 and my standardization of the system by means of an amboceptor titration has given excellent results.

thirty thousand complement-fixation tests on more than fifteen thousand sera sent me for diagnosis by the Wassermann and gonococcus complement-fixation tests I found that a large number of sera possessed some natural antisheep hemolysin. I, therefore, considered it advisable to make a series of tests by the method of Kaliski, and the absorption method of Rossi, for comparison with my own method which is a modification of the original Wassermann technic in that the total volume of the test is .5 c.c. A number of comparative Wassermann tests were also made with another laboratory which used the antihuman system of Noguchi.

All reagents were carefully standardized daily. The tests were set up in duplicate. Complement was fixed for four hours in the ice box with the crude alcoholic antigen, or for one-half hour in the water-bath at 37° C. with the cholesterinized antigen, and readings made according to the method advocated by Citron.[9] Sixty-seven sera were tested by the Kaliski method which gave no better results than my own method. In no case did sera treated by the absorption method of Rossi give complete fixation of complement in the Wassermann test where before tests on the same sera had been negative. In a few instances weak reactions became somewhat stronger, but in no case did they become positive.

In the gonococcus complement-fixation test I have found it advisable to use a very delicate system in order to obtain the best results and in these tests the natural hemolysin content of the serum did occasionally obscure complete fixation of complement. For example: a one plus obtained with a serum with a large natural hemolysin content sometimes gave a two plus or three plus after absorption and very seldom a four plus. No negative, however, became positive, though occasionally a negative became plus minus. Some sera became anticomplementary and in a few instances the antibody content of the serum seemed weakened by the absorption treatment in spite of the care taken to remove every particle of saline from the packed cells.

Remarkably constant results were obtained with the comparative tests made with the laboratory using the Noguchi method. Although readings were made on an entirely different scale in each laboratory there were inappreciable differences in the end results.

CONCLUSIONS.

In these studies, as in those of nearly all previous investigators, the presence of natural antisheep hemolysin was demonstrated in a large proportion (in this instance 51 per cent) of the sera tested. Contrary to the results obtained by many students of serologic problems, my experiments show that the effect of natural antisheep hemolysin in the practical operation of the Wassermann test is negligible. In no instance did this excess of natural antisheep hemolysin obscure complete fixation of complement. There seemed to be little difference in the results of Wassermann tests with sera from which the natural hemolysin had been removed and in the results of tests made by my usual method. The results with the Kaliski modification showed no improvement over those obtained with the usual test, and comparative tests made with the laboratory using an antihuman system showed no advantage over my own.

In the case of the gonococcus complement-fixation test, it would seem to be advisable to absorb the natural hemolysin from sera showing a very great ex-

cess, since stronger specific fixations have in some instances been obtained with sera treated by this method.

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THE WASSERMANN REACTION WITH LARGE AMOUNTS OF PATIENT'S SERUM*

By Anna I. van Saun, Albany, N. Y.

SOME serologic workers have attempted to show that more specific results can be obtained with the use of large amounts of human sera for the Wassermann test than with the amounts in ordinary use.

In this connection B. Fischer,[1] of the University of Rostock, Germany, cites the work of Ledermann[2] and von Kromayer Trinchese[3] as the basis for a series of Wassermann tests with large quantities of sera made by him at the Universitats-Hautklinik, in Rostock. For two years he tested upwards of 1300 sera, using the Kromayer modification; that is to say, quantities of sera ranging from .1 c.c. up to .4 c.c. and he came to the following conclusions:

A. Large amounts of serum are capable of

1. Changing a negative Wassermann reaction to a complete positive.
2. Changing a slight inhibition to a positive reaction.
3. Giving an indicator for the cessation of treatment. (The latter only to be discontinued when the largest amount of serum, .4 c.c. gives a negative reaction.)

B. All reactions giving complete inhibition of hemolysis with .4 c.c. of serum are specific.

Fischer made use of a serum control of .4 c.c. (the largest amount of serum used in his test) which, he asserts, was never anticomplementary. This seemed to me an unsafe amount upon which to rely as an absolute control for so large a quantity of serum, since it is well known that very large amounts of serum have in themselves a tendency to bind complement without the presence of a specific antigen.

For my work all complement-fixation tests are controlled, not only by the largest amount of serum used for diagnosis, but also by double the largest amount of serum used in the test.

I, therefore, thought it might be of interest to test a number of sera for the Wassermann reaction, not only with our standard amounts of sera, but also

*From the Division of Laboratories and Research, New York State Department of Health, Albany, N. Y.

with the amounts recommended by Fischer with the addition of a double control of .8 c.c. of serum in order to determine the possible specificity of this reaction. Seventy-four sera out of eight hundred specimens received during a period of one month were tested according to the Kromayer modification as worked out by Fischer, using .4 c.c. of serum as our largest diagnostic amount, with an added control of .8 c.c. of serum, as well as by our own method, based on the original Wassermann technic, making use of two quantities of serum, .2 c.c. and .1 c.c., and controlled by .2 c.c. and .4 c.c. of serum. No test was considered safe to read until the double controls .4 c.c. and .8 c.c. respectively had hemolyzed completely.

In almost every case complete hemolysis did not occur with .8 c.c. of serum in the double control tube in the Kromayer test even though it was left for an hour in the water-bath. Very frequently the .4 c.c. control hemolyzed so slowly as to make me doubt the specificity of a reaction obtained with specimens from cases having no history of syphilis and where my own test with smaller quantities of serum was negative. No negative became positive, and slight fixations with the ordinary amounts of sera could in few cases be considered specific when stronger with the largest amount of serum since the double control of .8 c.c. in nearly every instance did not hemolyze completely.

Sera from cases with positive histories which gave complete fixation of complement with the larger quantity of patient's serum and which showed hemolysis in the .8 c.c. control were also complete with the smaller quantities.

Fischer gives a great deal of clinical data which appears to check his results, but I believe from my experience that the Kromayer modification would be decidedly unsafe to use in a laboratory where there is no close connection with the clinical side of the cases, and where histories are frequently vague, unless a double serum control is put in with every test and the diagnostic tubes read only when the double serum controls are completely hemolyzed; a result which, according to the findings on the number of tests we have been able to examine with the Kromayer modification, would be difficult to achieve.

CONCLUSIONS.

1. The use of a large amount of serum does not, in my experience, change a serum giving a negative reaction to one giving a positive if a double serum control (.8 c.c.) is used and the result of the test read only when this control is completely hemolyzed.

2. In a number of tests I have found that the .4 c.c. serum control has been extremely slow to hemolyze, and has occasionally fixed complement completely. This result appears to point to a lack of specificity in a test depending on this amount for diagnosis.

3. Since large amounts of serum may of themselves bind complement without the addition of a Wassermann antigen, and since, in the above tests, in almost every instance, controls of double these large amounts of serum did not hemolyze completely, I do not consider the Kromayer modification a safe method to use for the practical examination of large numbers of sera.

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A METHOD FOR MAKING GRAPHIC RECORDS OF THE MOVEMENTS OF CERTAIN INTERNAL ORGANS

By D. E. Jackson, M.D., St. Louis, Mo.

THE instrument (Fig. 1) described in the following paragraphs has been used in dogs to record contractions of the stomach or pylorus (Fig. 2), the small or large intestine (Fig. 3), the uterus (Figs. 4 and 5), rectum, heart and bladder. In addition to these, the instrument can be used to register movements in the esophagus, and perhaps in the gall bladder, ureters, and spleen, although I have not as yet taken the trouble to thoroughly try the instrument out with the latter organs. These statements all refer to contractions recorded from the organs *in situ*, and in practically their normal positions. It is important that the blood supply and innervation to the organs from which records are being taken be not disturbed more than can be helped. In most cases this object is easily attained in using the instrument, for it has been designed with this end especially in view. In the abdomen the organs from which tracings are being

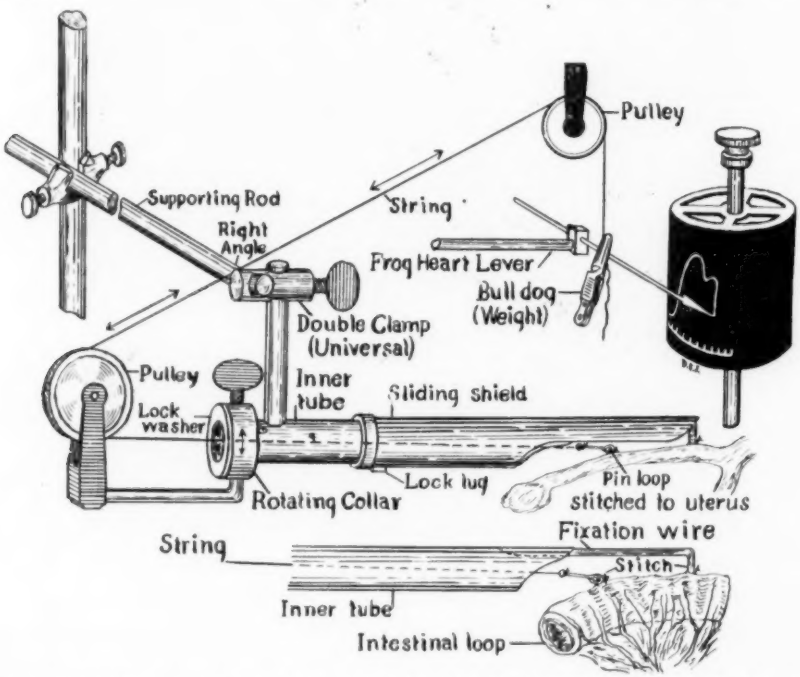

Fig. 1.—A diagrammatic representation of the method for using the instrument. (For discussion see text.)

obtained may be left almost, if not entirely, covered with the other viscera; and thus marked changes in temperature, drying, etc., are almost entirely avoided. Usually the abdomen can be closed by hemostats or stitches and the vitality of the animal is thus greatly conserved. In addition, shock is much less likely to

*From the Department of Pharmacology of Washington University Medical School, St. Louis, Mo.

occur than if the abdominal organs are considerably exposed to the air or otherwise extensively manipulated.

It is very easy to attach the instrument to the organs. In the abdomen this is done by first making a median longitudinal incision. In case the uterus is to be used one horn is then carefully exposed by moving the intestines up toward the diaphragm. Great care should be used not to touch the vessels or nerves going to the uterine horn. One may readily avoid these since they run along the posterior (caudal) edges of the organ. When one horn (usually the left) is brought into view, the flank of the animal is held up by a hemostat and

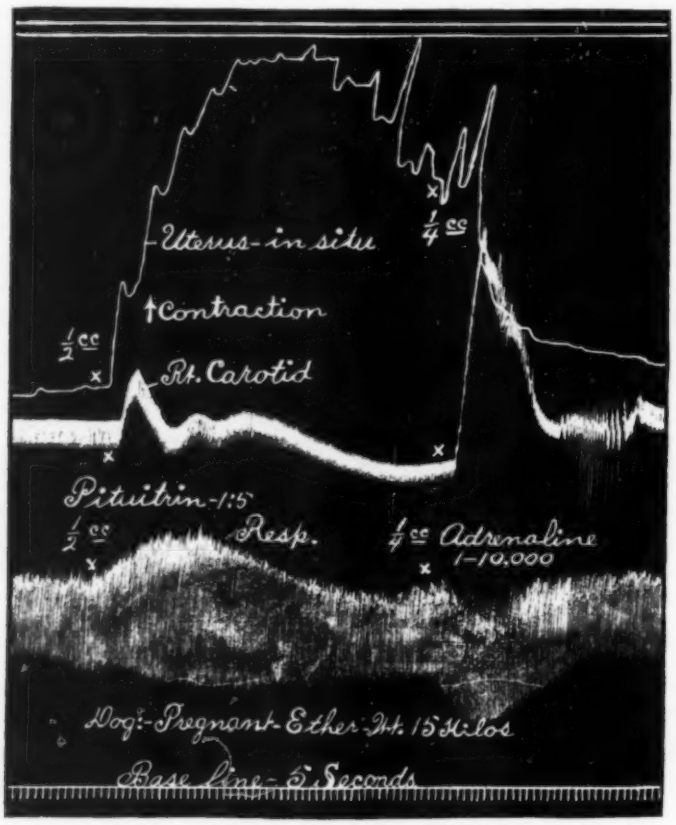

Fig. 2.—A tracing showing the manner in which the instrument records uterine contractions after pituitrin (and adrenaline).

an opening about one and one-half inches long is cut through the lateral abdominal wall about an inch below (caudalward from) the left ribs. The instrument is then clamped in a stand in such a manner that the two tube portions ("inner tube" and "sliding shield") should have a direction pointing caudalward, with reference to the animal, at an angle of about forty-five degrees from the median line, and inclined upward at a considerably smaller angle. The inner tube portion should then be about on a level with the exposed uterine horn. The tube portion of the instrument is then passed through the opening in the animal's flank by shoving the stand which holds the instrument closer to the animal. In

this manner the instrument is brought into a position parallel to and in immediate relation with the uterine horn. Before the instrument is inserted into the abdomen a long twine string carrying a pin with a ring bent on the end is passed over the pulley and through the length of the tube. When the tube is pushed into the abdomen the ring on the pin hook is then seized with forceps,

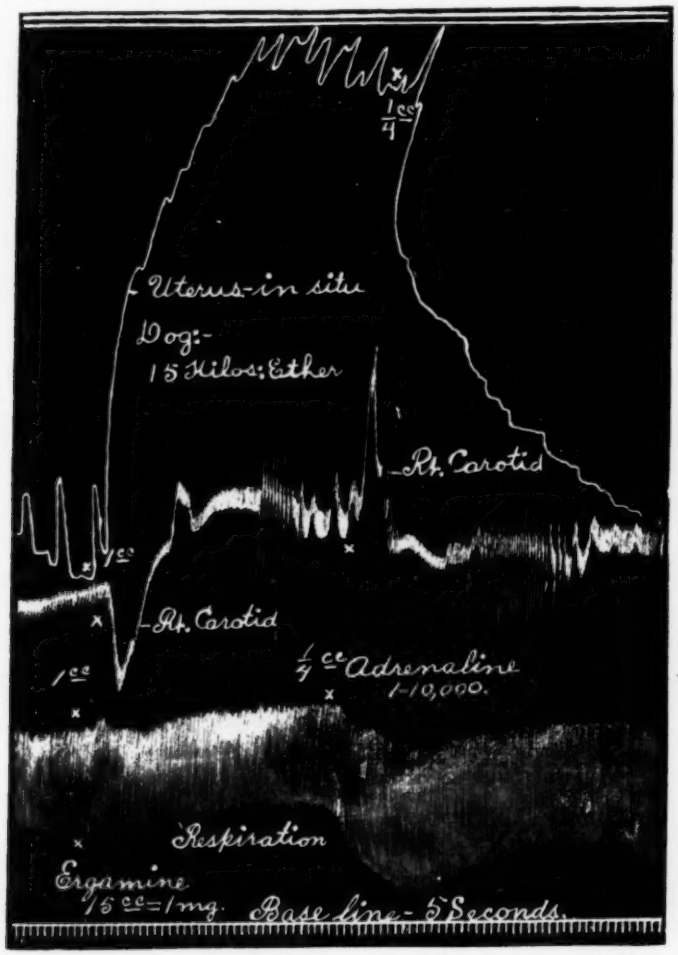

Fig. 3.—A tracing showing a record obtained with the instrument after ergamine (and adrenaline).

and with a single stitch made with great care with a fine, curved-pointed surgeon's needle the ring is tied to the upper edge of the uterine horn at a distance of about one and one-fourth inches from the bifurcation. During this process the "sliding shield" (Fig. 1) is slipped back on the inner tube so as to fully expose the "fixation wire." As soon as the ring or the pin has been attached, the bent end of the "fixation wire" is brought into position and attached with a single stitch to the tissues at the upper edge of the bifurcation. Thus the nerves and vessels to the horn need not be touched and the instrument is quickly and easily attached. The "sliding shield" is now slipped down over the "fixation wire" and the string is put on a little tension to see that a small mass of tissue

does not block its movement at the end of the inner tube. The abdomen is now completely closed, either with hemostats or stitches. The "sliding shield" serves to keep the other viscera from moving the uterine horn while records are being taken. The string is now passed over a pulley and connected to a frog heart lever which writes on the drum. The magnification of the lever should be about one to eight, or one to ten. The weight suitable for good sized bitches is about two or three ordinary bull dog clamps. It is important not to include too long a portion of the uterine horn between the two attachments. About one and one-

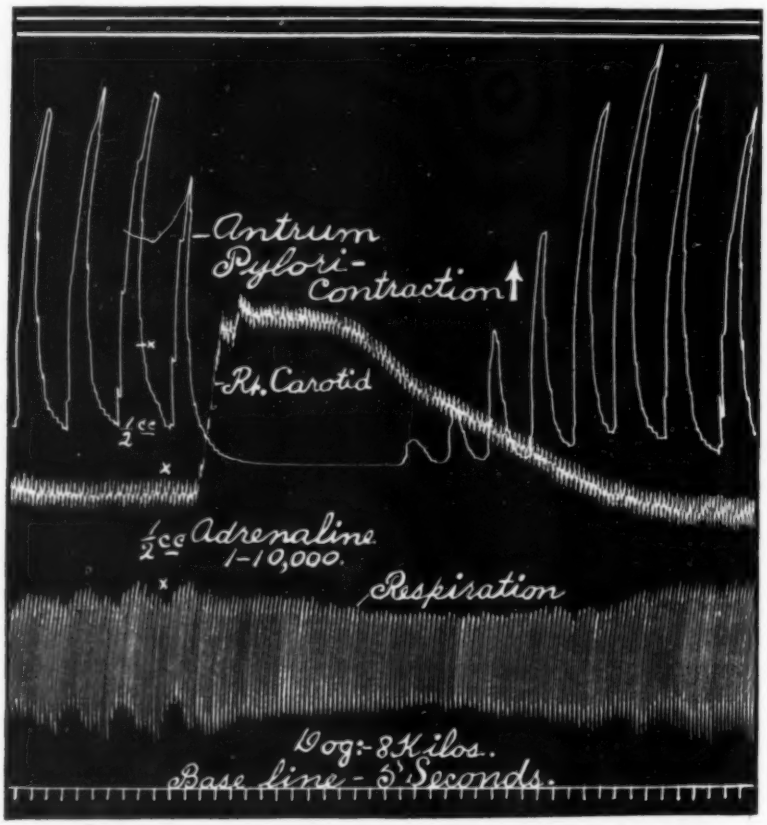

Fig. 4.—A tracing showing how the instrument may be used to record contractions of the antrum. The inhibitory action of adrenaline on the spontaneous contractions of the antrum is well shown.

fourth inches (or a little less) is approximately the length usually needed. When the record is started the chances are considerable that the uterus will already be in a condition of tonic contraction. To overcome this it is advisable to inject a small dose (¼ c.c. of 1:10,000) adrenaline to relax the organ. The drug produces a small primary contraction followed by marked relaxation (Figs. 2 and 3). A word of caution is necessary in regard to female dogs. Pups or young animals which have never borne young are not suitable for the experiment. Animals which are, or have been, pregnant previously are entirely satisfactory.

Records may easily be taken from almost any portion of the alimentary canal. For most parts of the stomach and intestines the instrument may be

readily brought into a satisfactory position through the median abdominal incision. Rarely one may wish to make a second small opening in the side of the abdominal wall for the insertion of the instrument. In practically all cases the abdomen should be securely closed after the instrument has been properly adjusted. It is of importance to note that records of either the longitudinal or the circular movements of the stomach and intestines can be obtained equally easily. This perhaps may be of use in studying the action of drugs, etc, on the various forms of peristalsis.

Fig. 4 shows a record obtained when the instrument was attached across, (i. e., transversely to) the antrum pylori. Spontaneous contractions of the antrum were occurring, but these were immediately inhibited for a brief interval by an injection of adrenaline. It is entirely feasible to attach two or three instru-

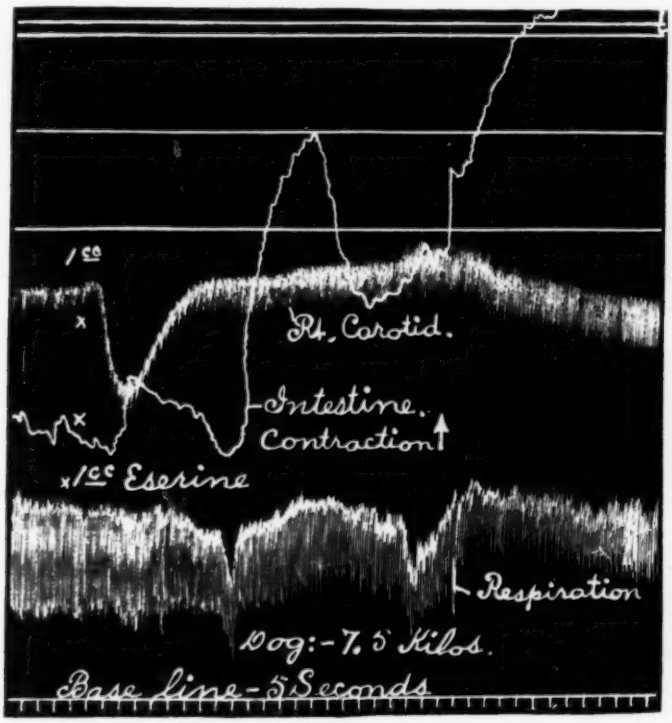

Fig. 5.—A tracing showing the action of eserine on the large intestine as recorded by the instrument.

ments to different portions of the stomach and thus obtain graphic records of the rate and character of its movements after vagus stimulation, etc.

Fig. 5 shows a tracing taken from the large intestine after an injection of eserine. It is to be noted that the large intestine, and particularly the lower portions, gives much larger and more constant contractions than does the small intestine. The record shown represents movements recorded from longitudinal attachments of the instrument. About one inch is usually a suitable length of intestine to include between the two stitches. The instrument may also be attached transversely to the intestine and two instruments may be used simultaneously if desired.

From the bladder records may be obtained by attaching the instrument either to the anterior, posterior, or lateral walls, or across the fundus of the organ, and these attachments may be made either longitudinally or transversely. To record the action of the heart the chest should be opened directly in the median line and throughout the entire length of the sternum. Four heavy strings are passed through the edges of the sternum, two on each side, in such a manner that the chest can be held open about two inches when the strings are tied down to the side of the operating board. The pericardium is now opened and the divided edges are attached by one or two stitches on each side to the edge of the chest walls.

The instrument is now placed over the heart in an almost horizontal position and pointing caudalward, i. e., "the fixation wire" is sewed to the apex of the ventricle. The ring on the end of the pin is attached to the base of the ventricle. The shield is now slipped down and the chest may be partially or completely closed, while the string passes to the recording lever in the usual manner. It is very desirable to have a perfectly regular artificial respiration, and it is advisable to give the animal a hypnotic (paraldehyde or chloretone) to be sure it will not revive and disturb the adjustments of the apparatus by slight movement during the experiment.

While I have so far had an opportunity to try this instrument only on dogs, I anticipate that it can be used equally well for cats or rabbits in the experiments for which those animals are suitable.

The wide applicability of this instrument, together with its comparative inexpensiveness (the device, exclusive of the heart lever and extra pulley, should cost approximately ten dollars; the extra pulley can be bought in large hardware stores for about fifty cents) has seemed to indicate that it might be of considerable use to teachers of pharmacology and laboratory workers in general; hence the publication of this brief note.

A SIMPLE METHOD OF OBTAINING BLOOD SERUM*

By M. G. Wohl, M.D., Omaha, Nebr.

A SATISFACTORY separation of serum from blood is desirable if not essential for various serologic reactions. Not all bloods, however, yield a good contracted clot allowing the serum to separate. It becomes necessary then to loosen the blood clot from the walls of the container by means of a platinum or glass rod. This procedure is undesirable as the introduction of the rod is liable to break up the red blood corpuscles and discolor the serum by the liberated hemoglobin; and again, it causes delay in obtaining the serum.

To meet these objections, we have been using in our laboratory paraffined containers. Blood which is quite adherent to the walls of an ordinary container will yield a clear serum when it is placed into a paraffined vessel. That

*From the Pathological Department, Nicholas Senn Hospital, Omaha, Nebr.

the paraffine does not alter the serum in any way, so far as the Wassermann and Widal reactions are concerned, we have proved by using controls of serums obtained in the conventional way. This method has been constantly used in our laboratory for the last three months and the results have been most gratifying.

TECHNIC.

Place a small piece of paraffine (half a gram is sufficient for an ordinary six inch serological test tube) into a container that is ready for sterilization, cork it and sterilize it. Upon removal of container from sterilizer roll it so as to cover its walls with the paraffine. It takes only a few minutes until the thin film of paraffine is hardened. To clean the container, rinse it with cold water until all the blood is removed, melt the paraffine and pour off. The excess of paraffine is removed by means of a gauze applicator. To the best of my knowledge paraffined containers have not been used heretofore for the above described purpose.

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Editor-in-Chief: VICTOR C. VAUGHAN, M.D.
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EDITORIALS

The Use of Poisonous Gases in the Present War

NOTWITHSTANDING the fact that the use of poisonous gases in war is distinctly prohibited by the Hague Convention, the Germans began the employment of this barbarous weapon early in 1915. At first it fell upon the unsuspecting Allied Armies like a blast from the furnace of death, but within a short time means of protection were found and since that time, the Allies have not hesitated to fight the devil with fire. To be efficient in war a gas must be not only toxic, but it must possess certain physical properties. It must be heavier than air, sufficiently dense to prevent rapid dissipation and it must retain its gaseous state within certain variations in pressure and temperature.

Poisonous gases so far employed in war may be divided into the following classes:

1. Those which are directly and immediately poisonous.
2. Those which produce slow death, by asphyxiation.
3. Those which put the victim out of action without doing permanent harm.

Those of the first class are hydrocyanic acid (HCN), arsenide of hydrogen (AsH_3), sulphide of hydrogen (H_2S), and phosphide of hydrogen (PH_3).

Those of the second class are chlorine (Cl), oxychloride of carbon

($C\text{-}O\text{-}Cl_2$) known as phosgene, acroleine ($CH_2\text{-}CO\text{-}CHO$) bromacetone ($CH_3\text{-}CO\text{-}CHBr_2$), chloropicrine ($CCl_3\text{-}NO_2$), methyl chloride of chloroform ($Cl\text{-}CO_2CH_2\text{-}Cl$) and methyl chlorosulphate ($SO_2\text{-}OCH_3\text{-}Cl$).

Some of the third class are chloracetone, bromacetone, iodacetone, bromacetic ether and iodacetic ether. Those of the third class are not known as poisonous gases, but as lachrymogenous. They cause an abundant flow of tears and for the time disable the men.

The Germans first used chlorine and the French replied by the use of phosgene (the oxychloride of carbon) which is said to be twenty-four times as effective as chlorine.

Poisonous gases are used, (1) in waves, (2) in hand grenades, (3) in shells. To these may be added the employment of liquid fire. Hand grenades filled with hydrogen phosphide and high explosives have been used. When exploded they emit a dense cloud of burning phosphorus. Chlorine and its compounds are usually employed in waves. On account of its lightness, phosgene is mixed with chlorine, and this mixture is known as "Collongite." When released from the tanks, the gas rolls along the ground and settles in the trenches and dug-outs. The effectiveness of the wave depends greatly upon weather conditions, notably upon, (1) wind, (2) humidity, (3) sunshine. The wind must be in the right direction and must not be too strong. A wind of about six meters per second or thirteen miles per hour is most suitable. A humidity of from forty to sixty per cent is most favorable. In bright sunshine and with low humidity, the gas is soon dispersed. Along the western front daily weather observations are made and forecasts recorded. The working of a gas attack is under a specially trained brigade of engineers. The tanks are so placed that the gas will reach the enemy and not fall into their own trenches. Since the trenches are tortuous and communicating, this is often no small task. The tanks are about ten inches in diameter and four feet long, weight when filled about 160 pounds and are fitted with folding handles. One great desideratum is to surprise the enemy and many devices have been resorted to for this purpose. Concentration of the gas is a matter of the greatest importance. When the Germans first used the gas it killed some who were ten kilometers to the rear. The liberation of a gas wave is accompanied by artillery firing and followed by an infantry attack. This must be wisely correlated or disaster will come to the attacking side. One purpose of the artillery fire is to cover the noise of the gas escaping from the tanks. Several plans have been devised for the early detection of the approaching gas. Strips of paper which are turned red by traces of chlorine are suspended in front of the trenches. A flame on the principle of a Bunsen burner plays upon a ring of metallic copper. The smallest trace of chlorine produces a green color.

Much effort has been expended upon devices to secure protection against the waves. High explosives have been tried in attempting to disperse the wave but without satisfactory results. Neutralizing gases and liquids have also proved ineffectual. Fire pots along the edge of the trenches were used for a while, but have been for the most part discontinued. These pots are ignited when the gas alarm is sounded and do something in the way of dispersing and lifting the gas. Bags filled with sawdust and ignited with oil have been used

for the same purpose. Sprays of hyposulphite, bicarbonate and carbonate of soda have been used. All attempts to secure collective protection against the chlorine gases have failed and for the most part have been discarded and reliance is now placed upon the individual mask.

The latest French mask is made of several thicknesses of gauze quilted together, consisting of a front and a crescent-shaped piece which, when the mask is adjusted, fits from just in front of the ears, down the cheeks and under the chin, the two horns of the crescent being in front of the ears. The front carries two goggles of celluloid fixed in place by metallic rings and inside rubber washers. The mask is held in position by elastic bands and tape. The band which goes around the back of the head holds the front firmly against the forehead, while that passing laterally over the head, attached to the crescents, pulls tighly up under the chin.

The gauze of which this mask is made is light brown on the outside and light green on the inner side. The gauze is impregnated with the neutralizing solution and furnishes complete protection for four hours when the gas is present in the proportion of 1:1000. It affords no protection against carbon monoxide. When not in use the mask is placed in a waterproof case and suspended like a haversack. The mask meighs 375 gm. and the cost is about sixty cents.

The Tissot apparatus, furnished the gunners, is more elaborate than the mask and permits better vision. It consists of a metal box about 14 x 6 inches, which carries the chemicals and is suspended between the shoulders. A flexible tube ending in a mask passes over the shoulder. The inspired air passes through the chemicals in the box and is purified. Valves are so arranged that the expired air is discharged outside the mask. The air first passes over water by which it is moistened, then sodium carbonate which neutralizes the chlorine, then sodium peroxide which supplies oxygen. The English have a similar apparatus which is carried over the left shoulder and is swung around to the chest when in use.

The only protection against carbon monoxide so far used is the Draegen apparatus, long used in mines. It consists of a cylinder of oxygen connected with a rubber bag with a tube terminating in a mouth piece. The apparatus is suspended from the neck and hangs in front. The nose is closed by a clip. Horses are protected by masks, and guns from the corroding effects of chlorine gas by vaseline or some heavy oil. The charging of shells with liquefied gas is a delicate operation, and must be done at low temperature. The No. 4 French gas shell contains the following mixture:

HCN	50 parts
Sn CI_4	35 "
As Cl_3	10 "
$CHCl_3$	5 "

The tin chloride seems to keep the hydrocyanic acid gas at proper tension. The arsenic is added as a smoke producer and the chlorofrom prevents crystallization. No. 5 shell contains phosgene and No. 12, bromide of benzyl. The last mentioned is especially valuable in "Counter Battery" work in which No. 12 shells are alternated with high explosives.

The liquid fire apparatus consists of a compressed air tank under a pressure of 600 kilos per square meter connected by an iron pipe with a valve with a second tank containing gasoline under a pressure of 10 kilos per square meter. From the gasoline tank a reinforced flexible tube passes under the right arm and ends in an iron projection with a pilot flame. The operator opens the valve between the two tanks in his back, lights the pilot by a friction slide and ejects the flame in any direction and up to 20 meters. With a continuous flame, one tank lasts about ten minutes and with an intermittent flame, much longer. The gasoline may be used as a spray and then ignited.

Professor Archard has prepared an official pamphlet on the use of poisonous gases from the medical standpoint. From this the following abstract is made.

Medical officers should familiarize themselves practically with wearing the masks in rooms filled with gas and in observations on animals both partially and fatally gased. Both French and English officers have this practical training. This is done both in rooms and in the open with conditions as nearly identical as possible with those of actual warfare. The first effect of small quantities of chlorine (1:1000) is irritation of the upper respiratory tract causing coughing and a sensation of suffocation. Rarely this may cause unconsciousness resembling chloroform anesthesia. Autopsies have been made on men found dead in the trenches, as the result of a wave, and showing no pulmonary lesion. This is an exceptional condition. In stronger concentrations of chlorine, men surprised, feel an intense suffocation, fall helpless and die in a few minutes. The face is dark, the lips greenish blue, the skin greenish with spots that are almost black. Experimentally dogs fall within 45 seconds and are dead within twice this time. On immediate autopsy the peripheral vessels do not bleed. The lungs do not occupy more than one-third the chest cavity. In color they are greenish gray and in consistency that of India rubber. On section the lungs are dry, bloodless and friable, having the appearance of cooked sausage. The trachea and bronchia are dry and gray. The heart is in systole, dry and rough. The right heart is slightly dilated and contains blood, which is thick and stains the hands brown. Other organs appear normal. Rapid death is frequent among the unprotected. In slower poisoning there is quickly developed an edema of the lungs and death may occur within an hour or after some days. One hears over the entire lung area, the subcrepitant rales of edema though this may be marked more or less by stronger bronchial rales. The heart sounds are heard with difficulty on account of the respiratory sounds. The median pulse may be imperceptible and the arterial tension falls way low. The individual often complains of severe pain in the base of the chest. Vomiting and purging may occur, but are not constant. Some die without the appearance of lesions and from severe intoxication. As a rule these are the older men.

Whatever may have been the beginning, on arrival at the hospital there is an incessant cough. Admission to a warm room and the recumbent position act as sedatives. Cold, speech, and movement intensify the cough. The temperature may be elevated one or two degrees for a few days but then falls to normal or below. Headache and asthenia are marked and may last for some weeks. As a rule the urine is normal but there may be suffusion followed by

albuminuria. A prognosis can not be safely made within three days but most of those who live this long recover under proper care. Old men are more seriously affected than the young.

One of the most common complications is a subcutaneous emphysema manifesting itself by a distension of the tissues, particularly at the base of the neck. Pulmonary gangrene is rare but gased men should be kept out of hospitals in which surgical gangrene has developed. Gangrene of the extremities sometimes terminates in death. Poisoning with phosgene is the same as that with chlorine but more serious.

The blood is black and tarry and does not run well. There is no deformity of the cells, white or red. The latter are increased in number and show no abnormality in hemoglobin content or spectroscopic appearance.

The main points in the treatment of those poisoned with chlorine or phosgene are the following:

1. Stop the poisoning by removal from the vitiated air or by protection with a mask.

2. Assist normal aeration by giving a pearl of ether, by the inhalation of oxygen or by inhaling very dilute ammonia. The last mentioned procedure must be resorted to with the greatest caution.

3. Restore normal circulation and blood pressure by taking from 300 to 500 c.c. of blood and repeating this with due caution if necessary by subcutaneous injections of caffeine or strychnine. Subcutaneous injections of large volumes of fluid, salt solution, alkaline or hyposulphite solutions should never be resorted to.

4. Relieve the obstruction of the bronchi by emetic doses of ipecac. Smaller doses of this drug may be continued for some days.

5. Allay the irritation by rest in a warm, moist air with the inhalation of oxygen. It should be understood that any use of oxygen is only sedative and not curative. One may be poisoned with chlorine in the midst of an excess of oxygen.

Hydrocyanic acid gas kills but does not wound. There is an odor of bitter almonds. A sense of constriction about the throat and head and then unconsciousness. The body stiffens with a few tremors and death results. Pathologic changes are not marked. The tissues are reddened somewhat by the combination of the poison with the hemoglobin. The masks give some protection.

First aid stations should have all openings away from the enemy and in a gas attack double cloths should be hung over the entrance and kept sprayed with a solution of carbonate and hyposulphite soda—the same as is used in the mask. The clothes of all who enter the station in a gas attack should be treated with the same spray. The usual formula for the neutralizing solution is as follows:

Water	1000 parts
Hyposulphite of Soda	220 "
Carbonate of Soda (Solvay)	175 "
or Crystalline	475 "

—*V. C. V.*